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DYSTONIA

I. HISTORICAL REVIEW; ANALYSIS OF DYSTONIC SYMPTOMS AND PHYSIOLOGIC MECHANISMS INVOLVED

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HISTORICAL REVIEW

During the fourteenth and fifteenth centuries epidemics of dancing occurred. They were apparently hysterical in nature, as far as can be judged from contemporary accounts. The condition finally came to be known as "St. Vitus' dance" because some of the victims recovered at the shrine of St. Vitus, in Saverne, France. This term was subsequently applied to all disorders characterized by hypermotility, whether they were neuroses or psychoses or were clearly the result of lesions of the nervous system. Paracelsus attempted an etiologic classification, differentiating "chorea imaginativa," the dancing sickness, from "chorea lasciva," caused by sexual desire, and chorea due to physical causes. Subsequently the pattern of the abnormal behavior was studied more thoroughly. Horst (1623) reported a case in which the abnormal movements did not resemble dancing but were described as simple movements of the limbs. Sydenham [1] (1685) distinguished for the first time the peculiar involuntary movements occurring in a nervous disease in children. But at the end of the eighteenth century major chorea, minor chorea and involuntary muscle activity (Wicke [2]) were not yet properly defined, and even epileptic phenomena were included with them. Bouteille,[3] in 1810, differentiated primary, secondary and tertiary chorea and described posthemiplegic chorea. Huntington [4] (1872) called attention to another well defined condition with choreic movements. The clinical work of Ziemssen (1877) and Wollenberg [5] (1898) and the pathologic investigations of Anton [6] (1896) and Bonhoeffer [7] (1897) established the basic knowledge of the group of choreic movements and the diseases in which they occur. Another type of phenomenon was defined by Parkinson [8] (1817) when he described shaking palsy and initiated the analysis of alternating tremor and rigidity. He referred to a case reported by de Sauvages,[9] in 1795, as one of *scelotyrbe festinans*. Credit for the establishment of athetosis as a distinct form of involuntary movement in nervous disease must be given to Hammond [10] (1871), who presented pathologic changes in 1 of his cases in a later edition of his textbook. In the following years many cases of disorders with athetotic movements were reported, as can be seen in the review of *l'athétose double* by Audry [11] (1892). Double athetosis became later a fairly circumscribed entity, after C. and O. Vogt [12] described status marmoratus of the striatum as the underlying pathologic equivalent, an assumption which has since been confirmed by numerous investigations (Lotmar [13]). Posthemiplegic unilateral athetosis

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

1. Sydenham, T.: Observationes medicae circa morborum acutorum historiam et curationem, London, G. Kettilby, 1685.

2. Wicke, E. C.: Versuch einer Monographie des grossen Veitstanzes und der unwillkürlichen Muskelbewegung, Leipzig, F. A. Brockhaus, 1844.

3. Bouteille, E. M.: Traité de la chorée, ou danse de St. Guy, Paris, Vinçard, 1810.

4. Huntington, G.: On Chorea, Med. & Surg. Reporter **26**:317, 1872.

5. Wollenberg: Zur Lehre von der Chorea, Arch. f. Psychiat. **30**:676, 1898.

6. Anton: Ueber die Beteiligung der basalen Gehirnganglien bei Bewegungsstörungen insbesondere bei der Chorea, Jahrb. f. Psychiat. **14**:14, 1896.

7. Bonhoeffer, K.: Ein Beitrag zur Lokalisation der choreatischen Bewegungen, Monatschr. f. Psychiat. u. Neurol. **1**:6, 1897.

8. Parkinson, J.: Essay on Shaking Palsy, London, Sherwood, Neely & Jones, 1817.

9. de Sauvages, F. B.: Nosologia methodica, Leipzig, sumpt. E. B. Schickerti, 1795.

10. Hammond, W. A.: A Treatise on Diseases of the Nervous System, New York, D. Appleton & Co., 1871.

11. Audry, J.: Étude de pathologie nerveuse: L'athétose double et les chorées chroniques de l'enfance, Paris, J.-B. Baillière & fils, 1892.

12. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systeme, J. f. Psychol. u. Neurol. (supp.) **25**:627, 1919-1920.

13. Lotmar, F.: Die Stammganglien und die extrapyramidal motorischen Syndrome, in Foerster, O., and

(Footnotes continued on next page)

was differentiated as a form caused by localized lesions, usually vascular, in the basal ganglia.

From these known forms of involuntary movements, chiefly double athetosis, another peculiar type was differentiated in the first decade of the twentieth century. At a time when athetosis was widely recognized as a symptom of an organic disease process of the brain, another form was again first described as hysterical. In 1908 Schwalbe [14] reported on a disease characterized by "tonic contractions with hysterical symptoms," and Ziehen,[15] enlarging the large but ill defined group of disorders known as *degenerative Krampfneurose*, added a new form which he called *Torsionsneurose*. Oppenheim,[16] elaborating his own observations and those of Schwalbe, inaugurated the term "dystonia" in 1911 and recognized "dystonia musculorum deformans" as an organic disease of the nervous system. Motor disorders constituted the cardinal symptom of the disease, defined as an alternation between hypotonia and a tendency to tonic muscle tensions, the latter being brought on most intensively by the locomotor functions of walking and standing. The occurrence of pronounced lordosis in the majority of his cases led him to suggest the name dysbasia lordotica progressiva as an alternative.

Almost twenty years before the description of Schwalbe and Oppenheim, Gowers,[17] in 1893, described the same symptoms in a case of so-called tetanoid chorea.

> There was tonic spasm which was continuous and varied by paroxysmal attacks of similar but more intense spasm . . . the arms were extended, pronated and rotated inwards, so as to bring the back of the forearm outwards while the fingers were generally slightly flexed at all joints; the feet being overextended in talipes equinovarus and the toes were flexed. At times the spasm of the hip became flexor so that the extended legs were raised off the bed. The muscles of the trunk were also involved in the spasm.

Similar symptoms had previously been observed in cases of double athetosis, namely, the occurrence of movements of the trunk and the proximal parts of the extremities differing somewhat from athetotic movements (Ross, d'Adversen, Kurella and others, cited by Audry [11]).

In the numerous reports following the description of dystonia by Schwalbe and Oppenheim, the peculiarities of the motor disturbances were analyzed, and attention was called to the onset in childhood and the occurrence of the disease in families of Jewish-Russian descent. Features particularly striking to the observer suggested new names, such as tortipelvis and progressive torsion spasm. Eventually, Mendel,[18] in a survey of all cases recorded up to 1919, summarized the significant clinical data and created the name "torsion dystonia." He differentiated this disease from other types of involuntary movements, such as hysteria, double athetosis, chorea and myoclonus and expressed the opinion that it constituted a morbid entity. At this time "dystonia" was defined as a disease entity on the basis of clinical observations alone; the responsible cause or causes were unknown, and specific pathologic processes were not recognized. The brain of the patient described by Thomalla [19] had been examined, but the lesions observed were used by Mendel merely as evidence for the presence of an organic disease process localized in the basal ganglia.

The situation became more complicated after the appearance of encephalitis lethargica and the frequent occurrence of postencephalitic states in the 1920's. The same symptoms as those thought to be characteristic of dystonia of unknown origin could be observed in a disease which was recognized as a clinical and pathologic entity. Furthermore, in the case of Thomalla, with the symptoms of dystonia, the lesions characteristic of Wilson's disease were present in the basal ganglia. These and other observations on cerebral lesions of well known origin (birth injury; carbon monoxide poisoning) produced doubt as to the concept of a morbid entity "dystonia" and suggested that various cerebral processes might be responsible for the appearance of dystonic symptoms. At the meeting of the International Neurologic Association in Paris (1929), Wimmer [20] concluded:

> Pathology has not been able to bring evidence that torsion dystonia is a disease entity. Dystonia as a

Willmanns, K.: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, Berlin, Julius Springer, 1926, no. 48; Das extrapyramidal motorische System und seine Erkrankungen, Fortschr. d. Neurol., Psychiat. **3**:245, 1931; Symptomatologie der Erkrankungen der Stammganglien, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5.

14. Schwalbe, W.: Eine eigentümliche tonische Krampfform mit hysterischen Symptomen, Inaug. Dissert., Berlin, G. Schade, 1908.

15. Ziehen: Ein Fall von tonischer Torsionsneurose, Neurol. Centralbl. **30**:109, 1911.

16. Oppenheim, H.: Ueber eine eigenartige Krampfkrankheit des jugendlichen Alters (Dysbasia lordotica progressiva, Dystonia musculorum deformans), Neurol. Centralbl. **30**:1090, 1911.

17. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1893.

18. Mendel, K.: Torsionsdystonie, Monatschr. f. Psychiat. u. Neurol. **46**:309, 1919.

19. Thomalla, C.: Ein Fall von Torsionsspasmus mit Sectionsbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **41**:311, 1918.

20. Wimmer, A.: Le spasm de torsion, Rev. neurol. **1**:904, 1929.

syndrome is in no way pathognomonic; it occurs with Wilson's disease, pseudosclerosis, athetosis, Parkinson's disease and Huntington's chorea.

In 1922 Wechsler and Brock [21] had already expressed the opinion that dystonia, double athetosis and Wilson's disease could not be differentiated in some instances, and Jakob [22] (1932), after an anatomic study of 3 cases, concluded:

> . . . Whether torsion dystonia is only a syndrome occurring with different disease processes in the brain or whether there is a morbid entity "dystonia" cannot be definitely decided. It is too early to differentiate distinct diseases.

However, in the last comprehensive description of torsion dystonia, in 1936, Mendel [23] stated:

> Torsion dystonia is a well defined syndrome, like Ménière's disease. In the same way in which exophthalmic goiter can be separated from the other forms of hyperthyroidism, so a distinct position must be conceded to dystonia. With this in mind, the cases of dystonia must be included in one disease group.

Mendel did not mention in 1936, as he did in 1918, the concept of a morbid entity.

In a symposium on the basal ganglia, at the meeting of the Association for Research in Nervous and Mental Disease in 1940, the problems of dystonia were referred to in some papers. Goodhart,[24] in explaining the various types of motor disorders, spoke of "cases of the dystonic group" and of "dystonic movements" and illustrated "some of the difficulties met in making a definite diagnosis between dystonia, psychogenicity and chronic degenerative chorea." Phelps [25] and Carlson,[26] in their papers on retraining and reeducation, referred only to cases of athetosis. They apparently assumed that cases of dystonia fell under the same heading. Bucy,[27] in speaking of choreoathetosis, stated:

> The term indicates an ill-defined group of abnormal involuntary movements. . . . Such a definition includes a variety of movements denominated as those of chorea, athetosis, hemiballismus, acute hemichorea, dystonia, torsion spasm, etc. etc. . . . It is obvious that accurate terminology is desirable but it has not seemed possible to achieve such a precision in the present state of ignorance of the underlying pathology and physiology.

Alexander [28] expressed the opinion that there is no fundamental difference between athetosis and dystonia. Athetoid disturbance of the extremities is called athetosis; athetoid disorders of the axial parts of the body, including the neck and trunk, are termed torsion dystonia. He stated that in his experience with the congenital bilateral form of athetosis and dystonia the one condition was never present without the other. The maintenance of two names—athetosis and dystonia—has caused a certain degree of confusion in that it suggests that these conditions may be two different diseases. But "athetosis and dystonia are one and the same disease, although difference in localization of this disease may cause one or the other symptom." Alexander suggested that the two names be used to describe the clinical phenomena but that the disease entity as a whole be referred to under the one name "athetosis." The pathologic observations of Alexander will be cited later. In this connection I wish only to stress that he drew his conclusions from cases of congenital disease alone in which status marmoratus was present as the pathologic process. Putnam [29] included in the "athetoid syndrome" athetosis and dystonia, torticollis, ballism and hemichorea. Electromyographic studies by Hoefer and Putnam [30] provided means by which these symptoms may be distinguished from antagonist tremor, whereas a differentiation of the clinically different types of the athetoid syndrome, particularly athetosis and dystonia, seems not to be possible. According

21. Wechsler, J. S., and Brock, S.: Dystonia Musculorum Deformans with Especial Reference to a Myostatic Form and the Occurrence of Decerebrate Rigidity Phenomena, Arch. Neurol. & Psychiat. **8**:538 (Nov.) 1922.

22. Jakob, A.: Zur Frage der lokalisatorischen und nosologischen Auffassung der torsionsdystonischen Krankheitserscheinungen, Deutsche Ztschr. f. Nervenh. **124**:148, 1932.

23. Mendel, K.: Torsionsdystonie, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, p. 848.

24. Goodhart, S. P.: Cinematographic Demonstration of Types of Extrapyramidal Syndromes, with Remarks on Differential Diagnosis, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:494, 1942.

25. Phelps, W. M.: Evidences of Improvement in Cases of Athetosis Treated by Reeducation, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:529, 1942.

26. Carlson, E. R.: Treatment of Athetosis by Retraining, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:534, 1942.

27. Bucy, P. C.: Cortical Extirpation in the Treatment of Involuntary Movements, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:551, 1942.

28. Alexander, L.: The Fundamental Types of Histopathological Changes Encountered in Cases of Athetosis and Paralysis Agitans, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:334, 1942.

29. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29**:504 (March) 1933; Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, ibid. **39**:258 (Feb.) 1938; Athetosis, Yale J. Biol. & Med. **11**:459, 1939; Neurologic Aspects of Spasticity and Athetosis, New York State J. Med. **41**:1822, 1941; The Operative Treatment of Diseases Characterized by Involuntary Movements, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:666, 1942.

30. (*a*) Hoefer, P. F. A., and Putnam, T. J.: Action Potentials in Athetosis and Sydenham's Chorea, Arch. Neurol. & Psychiat. **44**:517 (Sept.) 1940. Hoefer, P. F. A.: Physiology of Motor Innervation in the Dyskinesias, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:502, 1942.

to Putnam, different cerebral disease processes serve as underlying causes, among which are birth injury, infections, injury to the brain and degenerative diseases.

SCOPE OF PRESENT INVESTIGATION

The last conclusions expressed by Wilson [31] show how problematic the pathogenesis of dystonia still is. He stated:

> When torsion spasm appears as a symptom, it is hardly anything else than a variety of athetosis, proximal rather than distal; when it occurs in a "pure" state pathology shows that at least some cases belong to lenticular disease.

In view of this statement, many questions remain to be answered: "Hardly anything else" could mean "not quite the same"; "pure state" is not defined, and "at least some cases" does not include the majority of observations. The situation might be clarified by a consideration of the manner in which the investigation of dystonia has previously been carried on. Clinical observations with predominantly descriptive methods have resulted in the sorting out of a group of cases with a peculiar symptomatology. The original concept of a disease entity proved to be unfounded, and dystonia has since been regarded as a syndrome which occurs in various diseases. In view of the numerous investigations of the last thirty years, it seems worth while to review the collected material, both clinical and pathologic. First, dystonic symptoms and their physiologic mechanisms must be defined. Diseases in which these dystonic symptoms appear must be analyzed with respect to onset, course and accompanying disorders. In this way, in a number of cases, the clinician will be able to make an etiologic diagnosis, such as postencephalitic state, Wilson's disease (hepatolenticular degeneration), injury to the brain, infection, poisoning, tumor and arteriosclerosis. Dystonic phenomena in such conditions do not belong to the dystonia group; they constitute only a symptom, dependent on the particular localization of the process in the brain. Such conditions should be designated, for example, as postencephalitic state or Wilson's disease with dystonic symptoms. Only the remaining disorders, which cannot be placed under one of the recognized disease entities, should be grouped together as "dystonia." Since such a preliminary grouping is merely negative, the discussion of the character of the disease and the possibility that "dystonia" is a morbid entity should be postponed until uniform clinical pictures can be correlated with definite pathologic processes in the brain.

31. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940, vol. 2.

Consequently, in the following investigation I shall begin by using this classification. The cases of 15 patients who have been under observation at the Neurological Institute with a condition diagnosed as dystonia will be analyzed, and all the available cases reported in the literature will be considered. With the help of cinematographic analyses and electromyographic studies, dystonic symptoms will be defined and their mechanisms explored (part I). All cases in which well defined dystonic symptoms were present will be studied in detail, with the use of all available data. After the cases of known disease entities have been excluded, the remaining "dystonia group" will be defined (part II). The pathologic changes associated with diseases exhibiting dystonic symptoms will be reviewed, after the cases described have been classified clinically in the manner just outlined (part III). Finally, after known cerebral disease processes have been differentiated, a correlation of specific pathologic processes with clinical peculiarities of the "dystonia group" will be attempted.

DYSTONIC SYMPTOMS

FILM ANALYSIS OF CLINICAL CHARACTERISTICS

Dystonic movements belong to the group of abnormal involuntary movements associated with nervous diseases, such as chorea, ballism, athetosis, tic and antagonist tremor. Such movements are intercalated in the normal motor patterns without recognizable reason. They appear purposeless to the patient and to the observer. There is "the absence of inhibition or control which is characteristic of all involuntary movements" (Hunt [32]); in other words, there is an "excess of motion," which disturbs the posture at rest. Simultaneous disturbance of coordination and change in muscular resistance to passive movements may be present, e. g., hypotonia in cases of infectious chorea or rigidity with antagonist tremor.

By analysis of moving pictures I differentiated various forms of involuntary movements and described their characteristics.[33] Two types of "amyostatic hyperkinesis" (accepting a term first used by Strümpell [34]) were differentiated: irregular movements, including myoclonia and tic

32. Hunt, J. R.: The Static and Kinetic Systems of Motility, Arch. Neurol. & Psychiat. **4**:353 (Oct.) 1920.

33. Herz, E.: Die amyostatischen Unruheerscheinungen, Leipzig, Johann Ambrosius Barth, 1931.

34. Strümpell, A.: Zur Kenntnis der sog. Pseudosklerose, der Wilson'schen Krankheit und verwandter Krankheitszustände (der amyostatische Symptomenkomplex), Deutsche Ztschr. f. Nervenh. **54**:207, 1916; Die myostatische Innervation und ihre Störungen, Neurol. Centralbl. **39**:2, 1920.

twitchings, chorea, ballism, athetosis and torsion, and regular movements, including antagonist tremor and myorhythmia, and hyperkinesis, characterized by a complicated pattern. The turning and twisting character of some irregular movements induced me to suggest the term "torsion," but because of their predominant occurrence in cases of dystonia the term "dystonic movements" is more convenient.

Athetotic and dystonic movements show definite similarities. For that reason dystonic movements have frequently been referred to as proximal athetosis. As in my previous analysis, the mechanisms involved in athetotic movements may be described first.

Athetosis.—Characteristic of athetosis is the course of a single athetotic movement. In a simple voluntary movement, as well as in a choreic movement, the moved part is continuously shifted from one position to another. The athetotic movement does not take the same continuous course from the beginning to the end of the movement. First, tightening and stiffening of the affected part set in without a visible excursion. After a while the movement starts, and then the movement of the part is usually continuous to the end point. In an athetotic extension of the big toe the protruding, tightened tendon of the extensor hallucis longus muscle could be seen in 2 frames before the proper athetotic movement of the big toe started. But the course of the athetotic movement is not always continuous, even after the proper movement has started. Particularly in movements with larger excursions, the moving part sometimes stays in an intermediate position for a period represented by a few frames. At the end point of the movement the position is usually maintained until the moved part relaxes. The time relations of these peculiarities can be studied by comparison of single frames of consecutive moving pictures (16 frames represent one second at usual speed, and 64 frames, one second at slow motion). The series in figure 1 shows an athetotic extension of the index finger. At *0* the index finger was tightened, and at *3* (in three-sixteenths second) the extension was completed. The extension was maintained for 14 frames (almost a second), until suddenly, between frame *17* and frame *18*, the index finger became visibly flaccid.

The time consumed by the athetotic movement, from the beginning of the movement proper to the end position, is not remarkably greater than that consumed by a comparable choreic movement. The athetotic movement appears slower only because the time which the tension consumes at the beginning and at the end of the proper motion is included in the calculations. There are surely resemblances between chorea and athetosis. But it is doubtful whether "the resemblances are more impressive than the differences" (Wilson,[31] Hoefer and Putnam [30a]). At any rate, real differences between the two kinds of involuntary movements are distinctly evident in the analysis of the two clinical phenomena. Athetotic movements consist not only of motion from one position to another but of a factor with a stiffening and tightening effect, which increases the tension of the affected moving part. The character of the latter factor will be discussed later. At this point tension means only a visible and sensible condition of the muscles involved in the involuntary movement. The two factors of motion and tension vary in intensity from one case to another. There is always an inverse relation between the degree of tension and the speed of the athetotic movement. The tension is more pronounced in slower athetotic move-

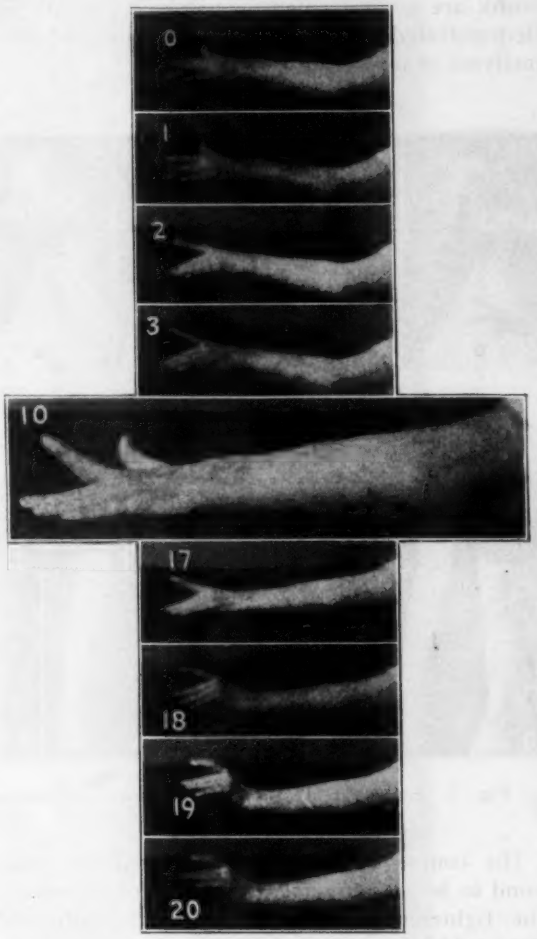

Fig. 1.—Athetotic extension of the index finger. Note the sudden release of tension between frame *17* and frame *18*.

ments and is less evident in the faster movements. Obviously, the activity of antagonist groups limits the rapidity of the movement.

Dystonic Movements.—Slow, long-sustained turning movements of the head and trunk and rotations of the upper or lower extremities were analyzed as dystonic movements. Besides these movements with a twisting effect, there were slow sustained tensions in the platysma muscle, the shoulder muscles, the pectoralis muscle and the muscles of the leg and foot. The head and trunk are most frequently involved, as will be demonstrated later in the description and film analyses of my own observations.

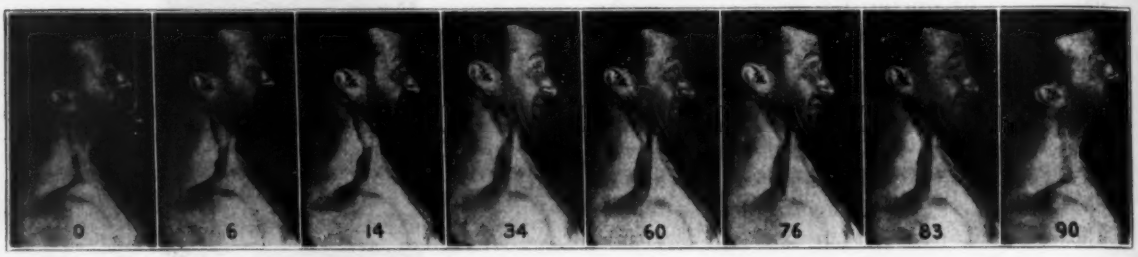

Fig. 2.—Sustained contraction of the platysma muscle.

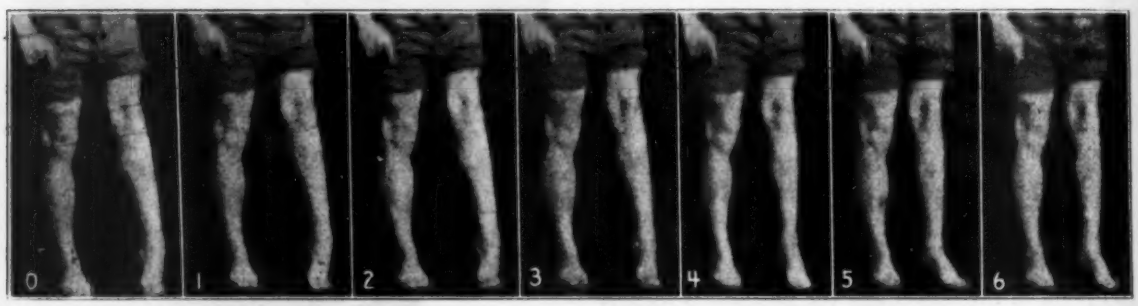

Fig. 3.—Sudden relaxation of long-sustained plantar flexion of the foot between frame *3* and frame *4*.

The course of the dystonic movements was found to be as characteristic as that of athetosis. The tightening and stiffening of the affected part could be seen before and during the movement and after the end of the motion proper, with the effect that the end position was maintained for a long time. In the film series shown in figure 2, contraction of the platysma muscle was completed in 6 frames, the end position being maintained from frame *6* to frame *83*, that is, almost five seconds, before the tension relaxed. How powerful the increase in tension may be can be seen in figure 3. The left foot was kept in extreme plantar flexion and inversion against the weight of the body for several minutes. As soon as the tension relaxed (which occurred suddenly, between frame *3* and frame *4*), the foot was pushed down in a small fraction (one sixteenth) of a second. Sustained tension may be interposed between other movements, with interruption and alteration of their course. The series in figure 4 shows the continuous record for a swinging movement of the right arm. From frame *1* to frame *8* the arm swings backward; from frame *9* to frame *13* the arm goes to a halfway position, and stays there from frame *13* to frame *23*. From frame *24* to frame *30* the forward swing continues. From frame *31* to frame *38* the arm swings backward; at frame *39* the forward movement starts again. During the course of an alternating swinging movement of the whole arm, tension arrests the swing for 10 frames and keeps the arm in an intermediate position. After the tension ceases, the alternating movements are continued.

The occurrence of particularly long-sustained tensions may be taken arbitrarily as the distinguishing characteristic of dystonic movements. The tensions are responsible for the slow course of the movements and the long-sustained intermediate or end positions. Between athetotic and dystonic movements there is only a quantitative difference in the degree of tension, that is, in the amount of simultaneous activity of antagonists. Both forms of abnormal involuntary movements, athetotic and dystonic, constitute a group of irregular sustained movements, characterized by tensions before, during and after the motion proper.

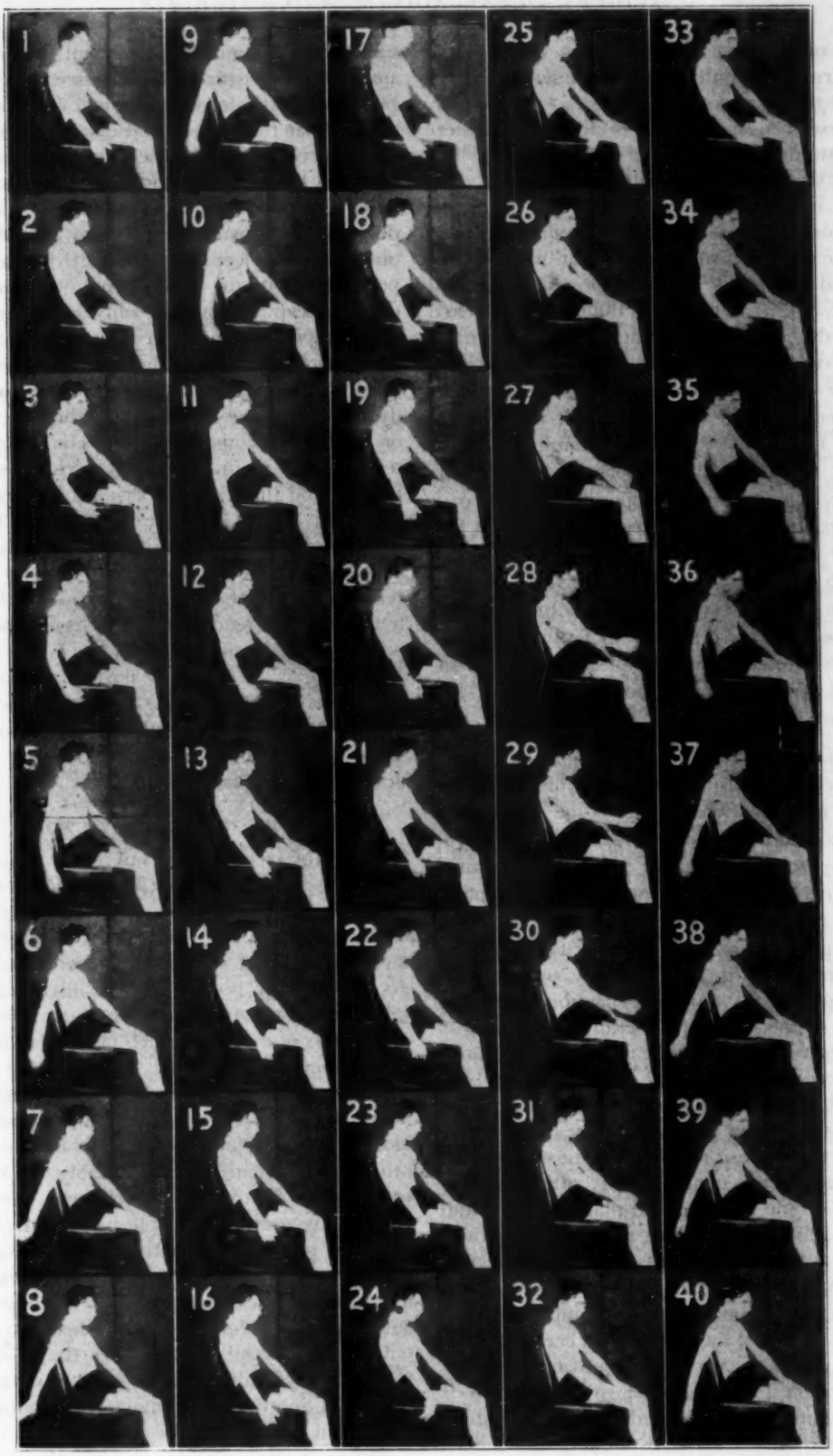

Fig. 4.—Arrest of swinging movement of the right arm by tension. In frames *1* to *8* the arm swings backward; in frames *9* to *13* the arm comes to a halfway position as it swings forward; in frames *14* to *23* it is arrested in this position; in frames *24* to *30* it continues to swing forward; in frames *31* to *38* it swings backward, and in frame *39* the arm starts to swing forward again.

Some observations indicate that various anatomic structures influence the tendency to tension and the hyperkinetic impulses. In case 13, to be described in part II of this study, there were dystonic movements of the left arm which showed extremely severe tension and little excess motion. Figure 16 *A* (part II [35]) shows the left arm in long-sustained extension and adduction. When the patient turned around and walked (fig. 16, *B* and *C* [35]), the arm was slowly flexed and adducted, and in all positions the hand was flexed and closed. A cortical operation was performed, and the right prefrontal arm area was excised. After the operation there was a striking reduction of tension; the arm was much more freely movable (fig. 16 *D* [35]), and involuntary movements of the hand and fingers appeared (*D*). The improvement after the operation in this case resulted particularly in decrease of tension. The reduction of tension after the anterolateral chordotomy in case 9 can be seen in figure 12.[35] The patient in case 2 [35] (compare the preoperative and the postoperative picture in figure 7 of part II) described the reduction of tension and the feeling of stiffness as the notable result of the chordotomy.

Dystonic Postures.—These peculiar positions, which occur in various combinations, will be described and illustrated later. One may better understand the mechanism involved in their production by reference to the significant features seen during the development of this crippling symptom as the disease progresses.

Drawing tensions in the back or the upper or lower extremities are first felt only subjectively, not infrequently as painful sensations. In the beginning of the disease this cramplike feeling is not accompanied by a visible motor effect. Later, interference with voluntary motor activity appears. The gait is hampered by tension in the leg or foot; "writer's cramp" may be an early sign. As the disease progresses, the position of the affected part becomes visibly altered. The foot may become inverted and plantar flexed and remain in this position when the patient is walking. At this time tensions result only in transient changes of position, which are maintained for a longer or a shorter period but are completely compensated. This fact has not always been realized, particularly in the case of longer-lasting postures. But in motion pictures taken over a period it could sometimes be observed how the posture was brought on by a corresponding movement and the end position was then maintained indefinitely. In the same way, the sudden disappearance of a presumably permanent, but only long-maintained, posture could be seen. Frequently postures are indeed maintained for such a long period that their onset and disappearance cannot be observed and are therefore completely neglected. In more advanced conditions the posture persists during the whole day, though the degree of distortion may vary, and disappears only during sleep. Persistent contractures in peculiar positions which are not reduced even during sleep are present only in advanced conditions with secondary contractures of tendons and muscles or changes in the skeletal system.

Thus, finer analysis of different degrees of dystonic postures proves that they are brought on by dystonic movements. The characteristic tensions are maintained over such an extremely long period that the impression of a motor act is eventually lost. If twisting activity of the trunk or extremities is maintained for seconds or for a few minutes only, the motor activity is registered as a dystonic movement. If the maintenance of the end position lasts for hours, the phenomenon is spoken of as a dystonic posture. In principle, a dystonic posture is merely an indefinitely sustained dystonic movement; it is the frozen product of such a movement. The same mechanisms are responsible for the production of the two phenomena.

MECHANISMS INVOLVED

From the facts brought out by the film analysis, one may draw some conclusions with respect to the different mechanisms involved in production of the varieties of irregular involuntary movements associated with various nervous diseases. As has already been stated, in all the abnormal involuntary movements there must be assumed an "excess of motion" which produces this abnormal spontaneous motor activity. In choreic movements this overflow of motor activity appears in pure form producing movements which closely resemble voluntary motor activity. In athetotic, and still more notably in dystonic, movements another factor changes the normal continuous course of simple movements, such as are seen in voluntary activity. "Excess of tension" results in stiffening and tightening of the affected muscles and produces changes in the course of the involuntary movements and maintenance of the end position. In the case of dystonic postures only finer analysis can demonstrate excess of motion; an almost continuous excess of tension prevails.

Figure 5 demonstrates graphically the degree of influence of the two factors in various involuntary movements. *Choreic movements* are due to excess of motion without remarkable excess of tension. *Athetotic movements* derive

35. Herz, E.: Dystonia: II. Clinical Classification, Arch. Neurol. & Psychiat., this issue, p. 319.

their significant features from the approximately equal participation of excess of motion and excess of tension. In some instances the excess of motion prevails over the excess of tension. *Dystonic movements* show a still more pronounced excess of tension, which prevails over the excess of motion. *Dystonic postures* show the influence of excess of tension in almost pure form, whereas the excess of motion is scarcely noticeable.

Electromyographic Studies.[36]—Patterns of innervation vary with the forms of irregular abnormal involuntary movements. Hoefer and Putnam [30a] gave an extensive analysis of the management of muscle contraction associated with these disturbances. In the studies with coaxial needle

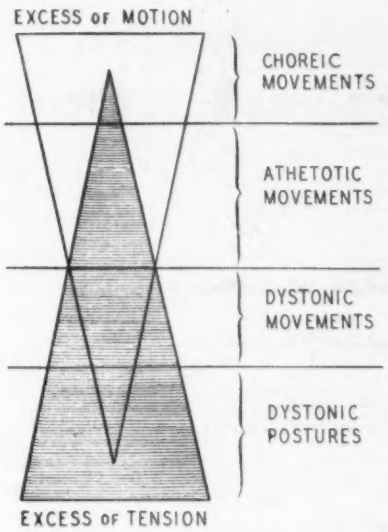

Fig. 5.—Distribution of "excess of motion" and "excess of tension" in different forms of irregular abnormal involuntary movements.

electrodes, local activity varied from single unit discharges to discharges of larger groups of units. Motor unit discharges were asynchronous and polyrhythmic, just as with normal voluntary innervation. The management of the antagonists was remarkable in that "antagonists were in almost constant, simultaneous innervation."

Obviously, this simultaneous activity of agonist and antagonist is responsible for the excess of tension observed in athetotic and dystonic symptoms. Oppenheim [16] stated that in cases of athetosis palpation revealed that antagonists were under tension. Wilson [37] found in mechanical tambour tracings that antagonists remained "definitely contracted." Hoefer [38] gave the following explanation:

> It is easy to conceive that movements must be arrested in a limb when all antagonist groups are simultaneously and maximally active or when a single muscle, such as the sternomastoid, by maximal sustained contraction holds the head and neck in an extreme position in relation to the trunk.

Hoefer, confirming Wilson's statement that "resemblances are more impressing than differences," did not differentiate between the different varieties of irregular involuntary movements. He spoke only of "more or less sustained irregular movements" and stated that "the simultaneous activity of antagonists may be steady or irregular in either muscle." From these statements it may be assumed that differences in types of innervation are present in the various irregular involuntary movements. It must be considered whether these differences in types of innervation are related to the more or less pronounced excess of tension in choreic, athetotic and dystonic movements.

Records will demonstrate the possibilities of differentiation.

Figure 6 shows records of a girl 14 years of age with Sydenham's chorea. Electromyograms were recorded with surface leads from the extensor and flexor groups of the forearm. The activity consists in short, irregular groups of waves or in bursts of longer duration in either the extensor or the flexor group. These records of electrical discharge found exclusively in one muscle group, as shown in *A*, *B*, *C* and *D* of figure 6, form 80 to 90 per cent of the recorded activity. In only a low proportion of instances did electrical activity appear in both antagonist groups, and in these instances the activity of one group was always predominant (fig. 6 *E*).

Figure 7 shows the records of a girl aged 13 years with Sydenham's chorea. The arrangement of surface electrodes on the extensors and flexors of the forearm was the same as that for the tracings in figure 6. Low voltage activity of shorter or longer duration was predominant in one group, while the antagonist did not show any activity (fig. 7 *A* and *B*). In one long-lasting burst both antagonists were involved, but the activity of the flexor group was much more intense and continuous than the activity of the extensor group (fig. 7 *C* and *D*).

In figure 8 are records of the electrical activity associated with athetotic and dystonic movements. These records were taken with surface electrodes. They confirm completely the statement of Hoefer and Putnam [30a] of the simul-

36. Dr. J. C. Price assisted me in this part of the paper, and Dr. Paul F. A. Hoefer gave me permission to use electromyographic records in his department.

37. Wilson, S. A. K.: Modern Problems in Neurology, New York, William Wood & Company, 1929.

38. Hoefer, P. F. A.: Innervation and "Tonus" of Striated Muscle in Man, Arch. Neurol. & Psychiat. **46**:947 (Dec.) 1941.

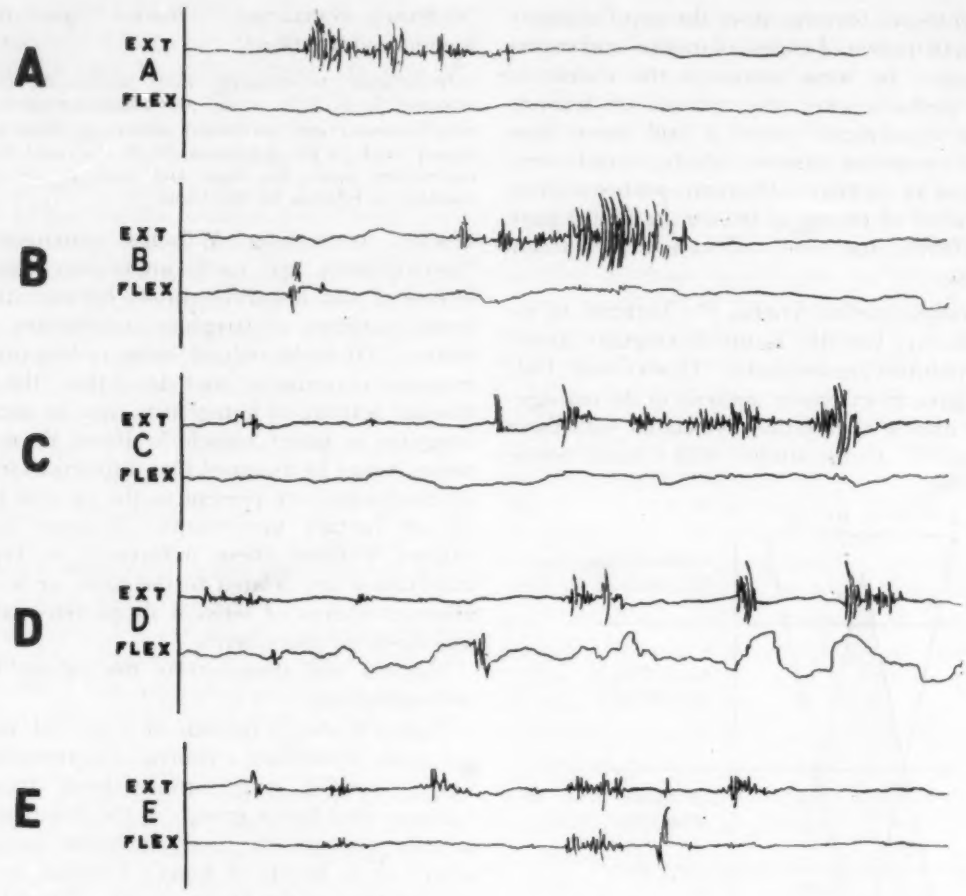

Fig. 6.—Electromyograms in a case of Sydenham's chorea.

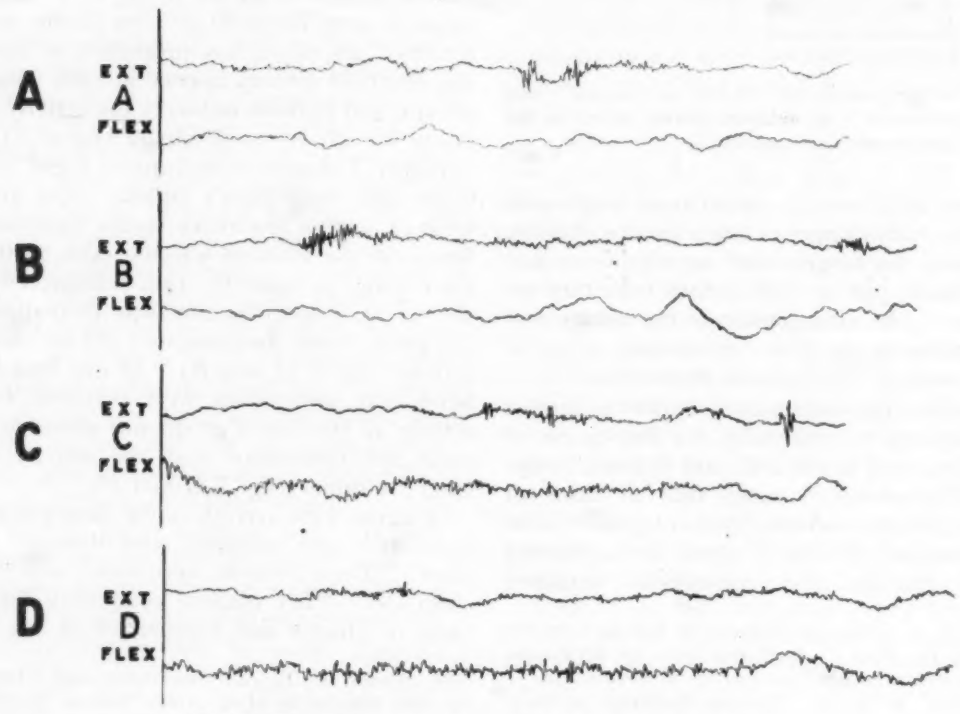

Fig. 7.—Electromyograms in a case of Sydenham's chorea.

taneous irregular innervation of the agonist and the antagonist. Records *A* (case 2 [35]) and *E* (case 4 [35]) show simultaneous activity in the flexor and in the extensor group of the thigh and simultaneous activity as that shown in record *B* was present almost exclusively. Record *D* (case 14) shows, again, simultaneous activity in the two antagonists, but the intensity of the flexor muscles

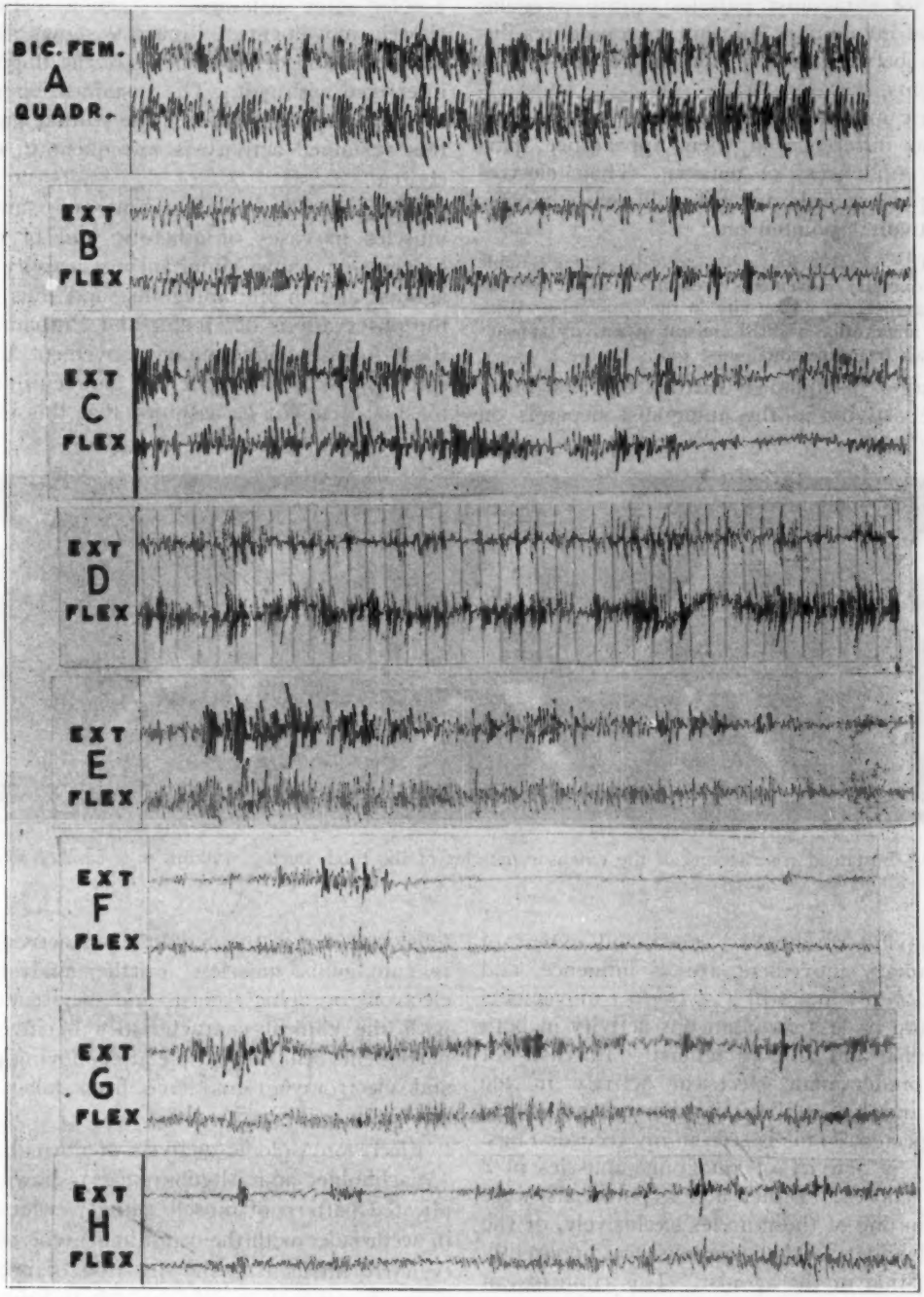

Fig. 8.—Electrical activity associated with athetotic and dystonic movements.

the forearm respectively. The intensity is equally maintained over a long period. The same simultaneous activities of equal intensity are found in a shorter burst (record *F*, case 4). During the severe hyperkinesis in case 11, such is higher than that of the extensor muscles. This is in accordance with the clinical observations (see protocol and film analysis), for the arm of the patient was in continuous tension and was held in a position of adduction at the shoulder

and of flexion at the elbow and wrist. Records *G* and *H* (case 4) show a continuous flow of activity in the flexor group, whereas the intensity of activity in the extensor group is fluctuating.

If one pays particular attention to the electrical activity of antagonist muscles during irregular abnormal involuntary movements, one notes differences between choreic and athetotic-dystonic movements.

Choreic movements and voluntary movements show no difference in their appearance, particularly no excess of tension. Their electromyographic records are alike; likewise, Hoefer and Putnam [39] pointed out:

> . . . The electromyographic records during simple normal voluntary movements presented only activity in the protagonist and no activity in the antagonist. With maximal innervation a small amount of activity appears in the lead from the antagonist too.

Altenburger [40] explained further that the onset of some activity in the antagonist depends on accompanying conditions; speed and extent of the voluntary movement are of influence, and loose (*lockere*) and stiff (*versteifte*) movements show more or less simultaneous activity in both the agonist and the antagonist. In cases of chorea predominant electrical activity in the agonist and less activity in the antagonist are to be expected. This is seen in my records (figs. 6 and 7) of activity of antagonist muscles in 2 cases of chorea. Either action potentials were present in one of the muscles exclusively, or the electrical activity of the antagonist was apparently less than that of the agonist. This confirms an observation of Hoefer and Putnam,[30a] who also found in a case of chorea "activity in the flexor muscles alone, while the extensor was at complete rest." Hoefer recorded in another case of chorea "simultaneous irregular activity, exactly as in athetosis." In a case of infectious chorea I noted some sustained contractions between the choreic movements. Figure 9 shows such sustained tension of the muscles of the thigh, which interfered with gait. The sustained extension in the swinging leg produced the stiltlike gait. But this sustained activity is infrequent in cases of chorea.

The records taken from two antagonist muscles in cases of athetotic and of dystonic movements show simultaneous activity in the agonist and in the antagonist and thus confirm the observations of Hoefer and Putnam.[30a] As these forms of involuntary movement are characterized by a greater or less degree of excess of tension, it might be assumed that this excess of tension is due to the simultaneous activity of the two antagonist muscles. Further analysis of the electromyographic records and their comparison with the clinical characteristics of involuntary movements will be possible after moving pictures and electromyograms have been taken simultaneously and synchronized.

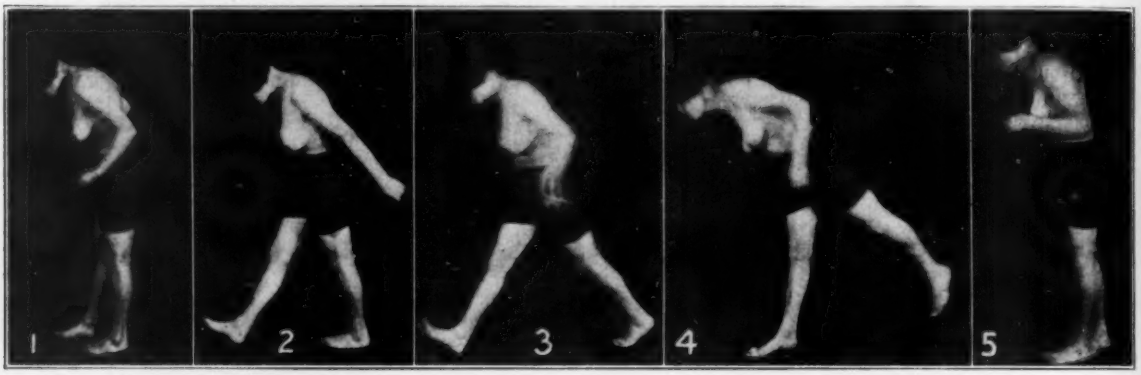

Fig. 9.—Sustained contractions of the extensor muscles of the thigh during walking in a case of Sydenham's chorea.

Electrophysiologic analysis of normal posture (Wachholder and Altenburger [41]) shows a complicated pattern of muscle activity, which varies in accordance with the conditions involved. Particularly intricate is the question of relaxation. Some, but not all, people are able to bring a part of the body into a relaxed position in which no activity can be recorded from either the agonist or the antagonist. The adaptation of the various

39. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201 (Aug.) 1939.

40. Altenburger, H.: Elektrodiagnostik (einschliesslich Chronaxie und Actionsströme), in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 3.

41. Wachholder, K., and Altenburger, H.: Willkürliche Haltungen, Arch. f. d. ges. Physiol. **212**:657, 1926.

mechanisms of posture to forces outside the body is made possible by different factors, e. g., by increase in number of the affected motor elements of a muscle or by a shift in activity from one part of a muscle to another. In the maintenance of posture, it is most important to "strut" joints, and thereby to connect two parts so closely that they form a steady support. This union is brought on by the simultaneous and maintained activity of antagonist groups of muscles. This stiffening activity in the maintenance of normal posture resembles the sustained tensions of dystonic postures. In both forms muscular activity is sustained for a long time.

Characteristic of dystonic posture is the appearance of such long-sustained muscle tensions without regard to any postural plan and with a peculiar distribution. Just as dystonic movements appear purposeless and interfere with motor behavior at rest and during voluntary activity, so tensions producing dystonic postures are not governed by the necessities of normal posture, but are mingled with postural motor innervations.

Figure 10 shows electromyographic records taken with surface electrodes from the muscles of the back of a patient with dystonic posture (case 3 [33]). The trunk and the upper part of the body were bent to the left when the patient was standing. Corresponding to this position there was continuous activity of the erector muscles of the left side of the trunk (records *A*, *B* and *C*). Most of the time the muscles on the right side did not show any activity. An occasional discharge from the right side (record *C*) may have been due to balancing movements. As soon as the patient lay in a prone position (record *D*, interruption at the vertical line), the abnormal posture and the bending of the trunk disappeared, and no electrical activity was found on either side. At the same time involuntary activity persisted in other muscles (the right trapezius muscle and the muscles of the right and left shoulders).

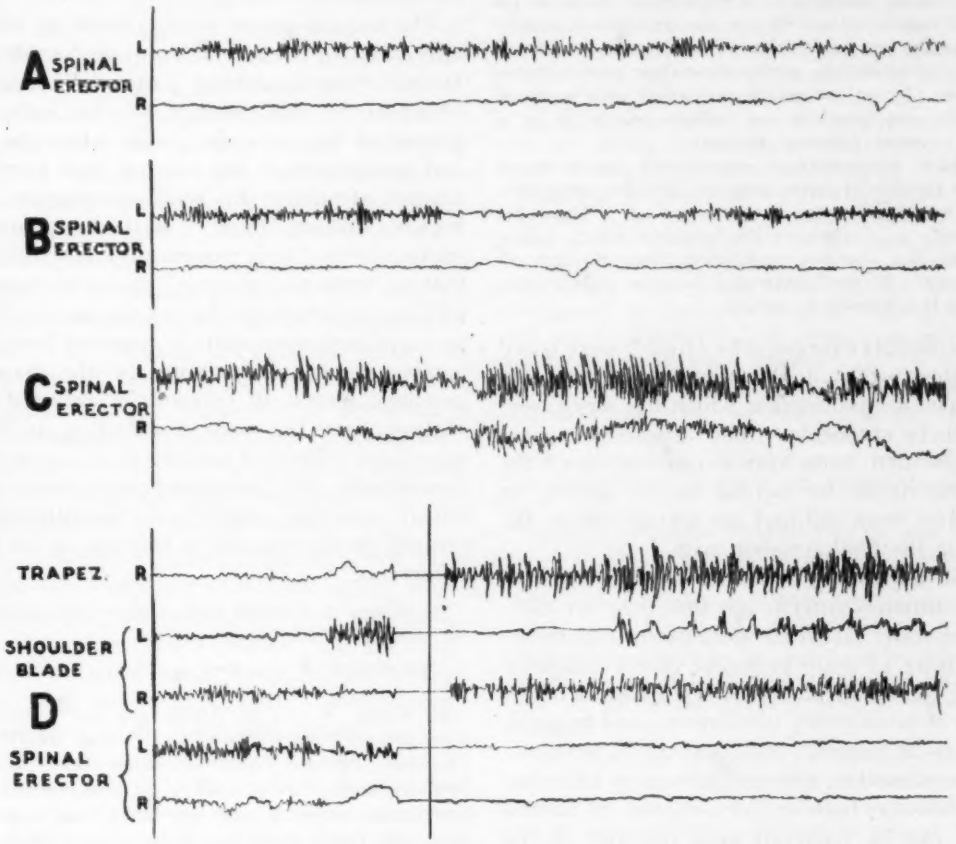

Fig. 10.—Electromyographic record of the muscles of the back of a patient with dystonic posture. After an interruption, shown by the vertical line, the patient lay in a prone position.

This record demonstrates that dystonic postural disorders are due to maintained motor innervations, as are dystonic movements. There is no important difference between these two phenomena; characteristic of dystonic posture is only the appearance of particularly long-sustained muscular contractions.

The mechanisms involved in the production of this abnormal involuntary motor activity are, of course, concerned in functions of the normal motor apparatus. One is used to regard these symptoms as "release phenomena," i. e., as excessive, exaggerated activity liberated by the destruction of higher, regulating centers, as suggested by Vogt.

Goodhart and Tilney [42] expressed the opinion that two principal mechanisms might be involved in producing the normally balanced motor function:

> . . . A kinetic mechanism is represented by a neural apparatus capable of correlating the impulses necessary to the production of purposive movements, attitudes and postures, ultimately giving these their proper motor expression. It, so to speak, prescribes and produces movements and postures for which reason it is a *kinethetic* system (causing motion).
>
> The static mechanism is represented by a neural apparatus capable of correlating the impulses necessary to the proper maintenance of postures. . . . The static mechanism . . . controls the postures which follow movements like shadows, stabilizing them through all their phases. In this sense and because it maintains posture, it is a *statothetic* system.

Similar concepts expressed by Hunt [32] were based on the theory of a double motor innervation of the muscle, an assumption which has since been proved to be erroneous. The various influences are transmitted from various structures of the brain responsible for normal motor activity to the anterior horn cell and are transferred to the muscle by the final common path.

Kinetic and static functions are so intricate and so intimately interwoven that they are difficult to separate. It seems more promising, therefore, to refer to more primitive motor functions in trying to explain the basic disturbances of the varieties of involuntary movements, and to speak of "excess of motion" and "excess of tension."

Excess of motion, which is present in all forms of hyperkinesia, both in nervous and in mental diseases, can be regarded as a disorder of the motor initiative. The normal motor behavior depends on internal (mental and physical) and external stimuli which result in a change from a condition of rest to one of motion. In hyperkinesias associated with mental disease the release of excess of motion produces a more complicated motor pattern. In nervous disease more primitive motor functions are released, and only patterns of simple movements and innervations are carried out. Kleist [43] asserted that the primitive innervations of abnormal involuntary movements associated with nervous disease are liberated constituents (*Bausteine*) of normal and synergistic movements.

The mechanism of tension, with its stiffening effect, is significant in normal motility also. Holmes,[44] in describing postural fixation, drew attention to this function: "Its influence is greater at the proximal joints when the weight and momentum of the moving limb particularly require steadying by tonic contraction of the muscles around them." If the frequently misleading term "tonic contraction" is replaced by that of "sustained tension," the same mechanism which was pathologically exaggerated in dystonic postures and movements is apparent here. Those long-sustained contractions of the trunk and proximal parts of extremities referred to by Holmes have the same distribution as dystonic symptoms. This, of course, is not an accidental coincidence; the preformed mechanism of sustained muscular activity is pathologically increased predominantly at the site of its normal occurrence.

Dr. Tracy J. Putnam gave advice and assistance in the writing of this paper.

710 West One Hundred and Sixty-Eighth Street.

42. Goodhart, S. P., and Tilney, F.: Bradykinetic Analysis of Somatic Motor Disturbances, Neurol. Bull. **3**:295, 1921.

43. Kleist, K.: Zur Auffassung der subkortikalen Bewegungsstörungen, Arch. f. Psychiat. **59**:790, 1918; Paralysis agitans, Stammganglien und Mittelhirn, Deutsche med. Wchnschr. **51**:1725, 1768 and 1813, 1925; Bewegungsstörungen und Bewegungsleistungen (Myostase und Psychomotorik), Naturwissenschaften **15**:50, 1927; Gehirn-Pathologie vornehmlich auf Grund der Kriegserfahrungen, Leipzig, Johann Ambrosius Barth, 1934.

44. Holmes, G.: The Cerebellum of Man. Brain **62**:1, 1939.

DYSTONIA

II. CLINICAL CLASSIFICATION

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NEW YORK

It has previously been pointed out that the diagnosis of "dystonia" has been indiscriminately applied to all cases in which dystonic symptoms appear. Dystonia defined in this way was, therefore, to be regarded "merely as a variety of extrapyramidal disease whose motor disorder is predominantly dystonic in order, rather than a distinct clinical entity" (Keschner).

In principle, the indiscriminate grouping together of conditions with different causes hampers further investigation. The concept of a cerebral disease entity should always be based on the occurrence of a well outlined constellation of clinical symptoms produced by a distinct pathologic process affecting certain structures of the brain. As long as the clinical picture of dystonia cannot be correlated with a definite pathologic lesion, the function of a preliminary clinical investigation is to establish clinical groups which are as homogeneous as possible; later one may try to correlate this preliminary clinical grouping with the pathologic lesions.

In the following 15 cases of patients who were examined and treated at the Neurological Institute of New York between 1940 and 1942, dystonic symptoms were present and the diagnosis of "dystonia" was considered. Motion pictures and electromyographic records were taken for analysis of the motor disorders. Detailed analyses of the films will illustrate the motor phenomena described. The onset, development and course of the disease were taken into consideration, and conclusions were based on all the clinical data available. Special attention was paid to certain distinct entities within the dystonia group.

REPORT OF CASES

CASE 1.—*History.*—J. W., a white man, was 24 years of age at the time of his admission. The family history was noncontributory. Delivery had been spontaneous, after a normal, full term pregnancy. His early development was normal.

At the age of 8 years he began to walk with his right heel raised from the ground. He was able at times to force the heel to the ground voluntarily, but the foot soon resumed an extended position. In the following month he began to have periods of contraction of the muscles of his right lower extremity, which produced spontaneous flexion of the thigh and leg, lasting for several minutes to a few hours; soon his leg remained permanently in a flexed position except when forced in extension. A year later the left upper and lower extremities were involved, and a few months later the right upper extremity was affected. At about the same time he began to have widespread movements of all the extremities, in addition to the tonic contraction, and during the succeeding years various muscles of the trunk and neck gradually became involved.

Beginning in 1926, over a period of several years, he underwent a series of operations to relieve the contractures at the hips, knees, ankles and right wrist. The involuntary movements and tensions persisted and greatly limited the patient's activity. But he managed courageously to overcome these difficulties, and could even use the typewriter. He became an accomplished linguist and spoke seven languages.

Examination.—Physical inspection revealed pronounced scoliosis of the spine, contractures of the extremities and operative scars. There was notable wasting of the lower extremities. The hand grasp was fairly good. The reflexes were normal, and there was no sensory loss.

Mental examination revealed that he was intelligent and alert and had made an excellent adjustment to his illness.

The results of laboratory tests were normal.

Operation.—A laminectomy was performed, and the anterior column between the second and the third cervical segment on the right side was cauterized. The motor roots of the second cervical segment were crushed bilaterally.

Film Analysis.—When the patient was standing (fig. 1 *A*), the head was hyperextended far backward, turned to the right and bent to the left. There were extreme lordosis and kyphoscoliosis, with turning of the trunk to the left. The right shoulder was higher than the left. The right arm was kept behind the back; the left arm was adducted and flexed at the elbow, and the left hand and fingers were flexed. The lower extremities were held apart and extended. Both feet were in plantar flexion and inversion. The patient had difficulty in keeping his balance; he swayed about; the twisting torsion of the trunk increased, and there were alternating flexion and extension of the left arm with swinging movements of the leg and the whole body. He was able to stand only for a short while and then had to be supported.

Slow motion pictures revealed slow, sustained twisting movements of the trunk and swinging movements of both arms at irregular intervals, turning of the head and alternating flexion and extension of the forearms and hands.

A close-up exposure of the head and the upper part of the chest showed that the twisted position of the

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head was long maintained (fig. 1 *B* and *C*). Then, simultaneous with the turning of the head to the right, there were sustained elevation of both shoulders and backward extension of the right arm. The end position was maintained for some time; then the tension was released again, and the head was first turned to the left. After a few moments the head was hyperextended and then bent far to the right and kept in this position. At the same time the trunk was bent forward. There were no involuntary movements of the face.

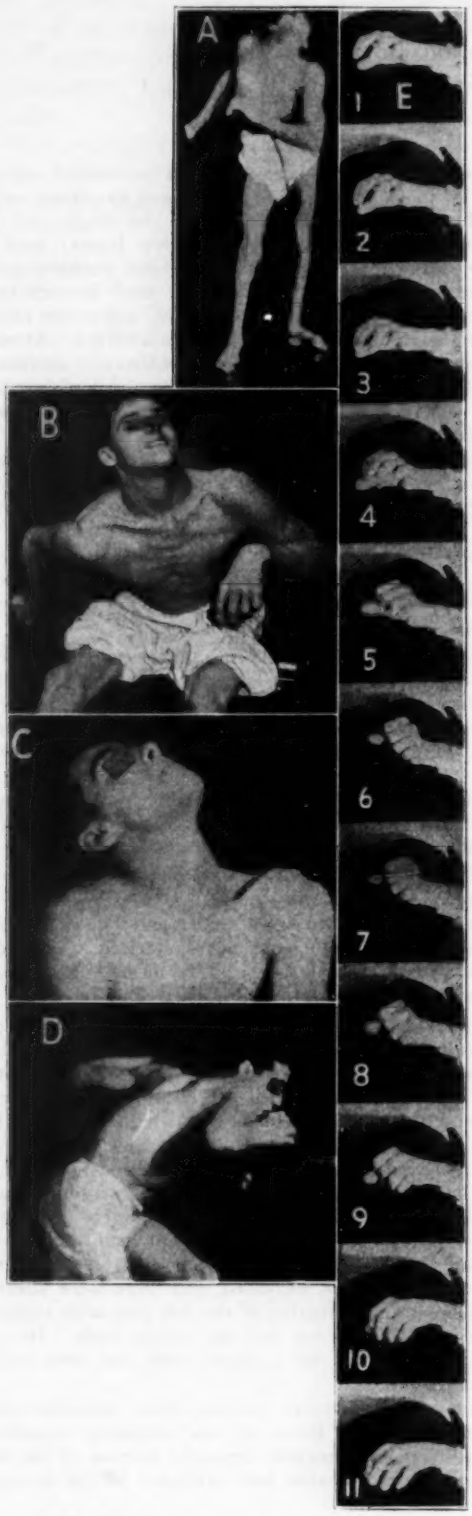

Fig. 1 (case 1).—*A*, patient standing; *B* and *C*, close-up view of head and upper part of body; *D*, patient drinking water; *E*, rapid opening and closing of hand.

A close-up view of the hands revealed three kinds of motor phenomena:

1. Long-sustained dorsiflexion of the wrist and long-sustained extension of the fingers at irregular intervals. The periods of maintenance in the end position were always different, as were the intervals before onset of the tensions.

2. Alternating flexion and extension of the hand and fingers at apparently irregular intervals. Figure 2 shows alternating flexion and extension of the left hand at the wrist. Flexion was always followed by extension, but the end point of extension was maintained for varying lengths of time. The single frames showing extension, flexion and the maintained end position were counted and the data outlined in figure 3. The alternating units (extension and flexion) followed one another at completely irregular intervals (5—15—5—7—14 frames).

3. Rapid opening and closing of the hand. During the closure there was the synergic dorsiflexion of the hand at the wrist. Figure 1, series *E*, shows closing of the hand in three frames (between frame *4* and frame *6*), instantly followed by opening, which appears in three frames (between frame *7* and frame *10*). The whole cycle was completed in less than half a second.

A close-up view of the lower extremities showed alternating movements of the left leg and swinging movements of both legs, interrupted by long-sustained extension of the lower part of the right leg, with flexion at the hip. The feet were usually kept in a pes cavus position—in extreme plantar flexion and inversion. The plantar flexion relaxed sometimes for a few moments, especially in the left foot. There was extreme plantar flexion of the toes.

The patient was skilful in drinking water out of a paper cup (fig. 1 *D*). When sitting on a chair, he tried to keep his body as steady as possible by grasping the back of the chair with the left hand and pressing the upper part of his body against the table.

Motion pictures taken after operation showed no significant change in the position of the head, trunk and extremities. No visible difference in the tensions or the involuntary movements was observed.

A child of a healthy family, without a history of injury at birth, developed perfectly up to the age of 8 years, when motor disorders began. Sustained tensions in the right foot were the first symptom. They came on as associated movements during walking and produced a peculiar position of the foot. Gradually the same disorder affected the whole right lower extremity. Then the postures produced by the tensions were maintained from several minutes to a few hours; later they became permanent, and finally the trunk, neck and all four extremities were involved.

In addition to these dystonic movements and postures, more rapid involuntary movements appeared and interfered with voluntary action.

Analysis of the films revealed them as alternating movements in which flexion and extension of the forearm, hand or fingers followed one another. But, unlike the regular repetition of alternating units (consisting of flexion and extension), as observed in antagonist tremor, the units of these alternating movements appeared at irregular intervals. In order to differentiate this form of alternating movements from antagonist tremor, it should be called "myorhythmia."

Very rapid, ticlike twitchings could be differentiated as another form of involuntary movements. Opening and closing of the hand occurred in less than half a second. These twitchings came on occasionally, at completely irregular intervals.

The symptoms consisted exclusively of this involuntary motor activity. Neurologic examination did not reveal any other abnormality. From the clinical point of view one may speak of an elective systemic disease which affects exclusively motor relaxation and the appropriate distribution of motor innervation. No cause responsible for the development of this steadily progressive process could be determined.

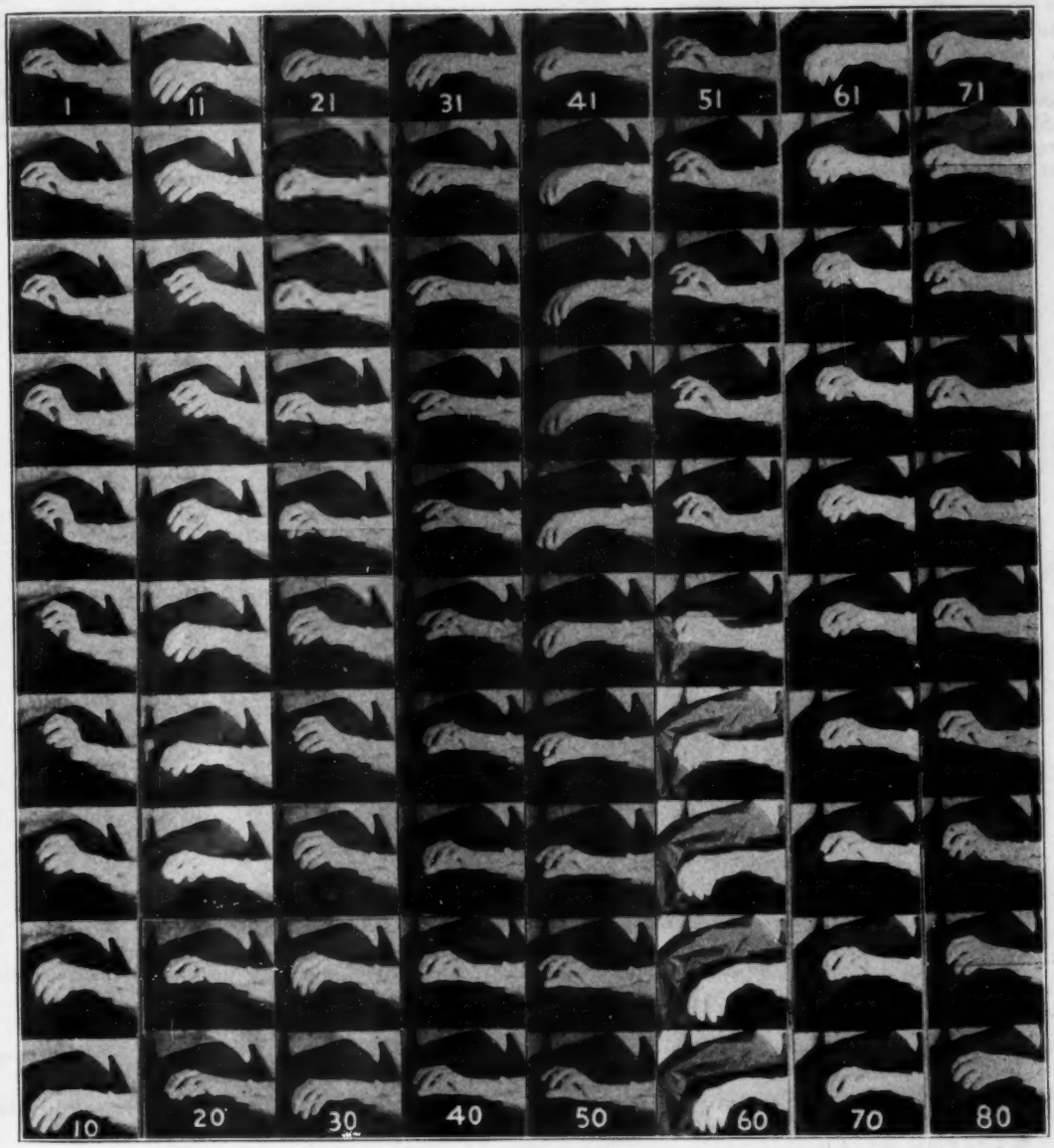

Fig. 2 (case 1).—Alternating flexion and extension of left hand at wrist.

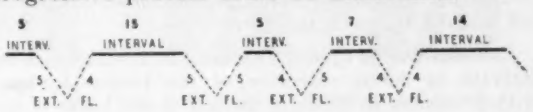

Fig. 3.—Evaluation of alternating movements in figure 2. (Note the irregular intervals [5—15—5—7—14 frames]).

The anterolateral chordotomy did not visibly influence the involuntary movements or the posture. Differences between the side of operation (right) and the left side could not be seen in the motion pictures.

Case 2.—*History.*—B. R. was first admitted to the hospital in 1930, when she was 10 years old. At this time she gave a history of onset of deformity of the left ankle with limp in November 1929. There were also attacks of rigidity, mild choreiform movements of the hands and dystonic movements of both lower extremities. She stood only with support. There was pronounced scoliosis with the convexity to the right.

She was again admitted in 1937, with a history of progression of the disease during the interval. There was deformity of the right side of the chest, with thoracic kyphosis and scoliolordosis. The head was pulled back and to the right. Choreoathetoid movements of the entire body were noticed, which were variable in excursion, amplitude and degree and were more severe when she was excited and apprehensive. The hyporeflexia was of equal degree on the two sides.

In the interval since this admission the bodily deformity has increased. The patient is now agonized by the involuntary twisting of the head and the contraction of the left lumbothoracic region, which causes the left scapula to reach the pelvic crest.

Examination.—Physical examination revealed extreme increase in dorsal extension of the lumbar lordosis, with prominent kyphosis to the left in the lower dorsal region and rotation of the pelvis to the left, so that the left scapula rested on the left ilium when the patient sat up. There was angulation of the left portion of the thoracic cage along the anterior axillary line, so that this side of the chest was collapsed laterally. She walked by hunching along two or three steps at a time, when she was unable to support herself longer. She could go rather rapidly in a sliding run, better than in walking. There was notable increase of strength in the muscles of the upper extremities, the shoulder girdle and the neck. The muscles of the legs were decreased in bulk, but strength was better than the size would lead one to suspect. The voice was of variable huskiness, but words were clearly enunciated at times. The only reflexes elicited were the abdominal reflexes, a weak biceps reflex in the right arm and a normal ankle response on the right. The pupils, when observed obliquely in indirect light, had a green appearance, but no Kayser-Fleischer ring was noted. The tongue was extremely long, and the patient was able to protrude it farther than normal; the jaw was opened wider than normal. The fully extended tongue could be bent backward on itself.

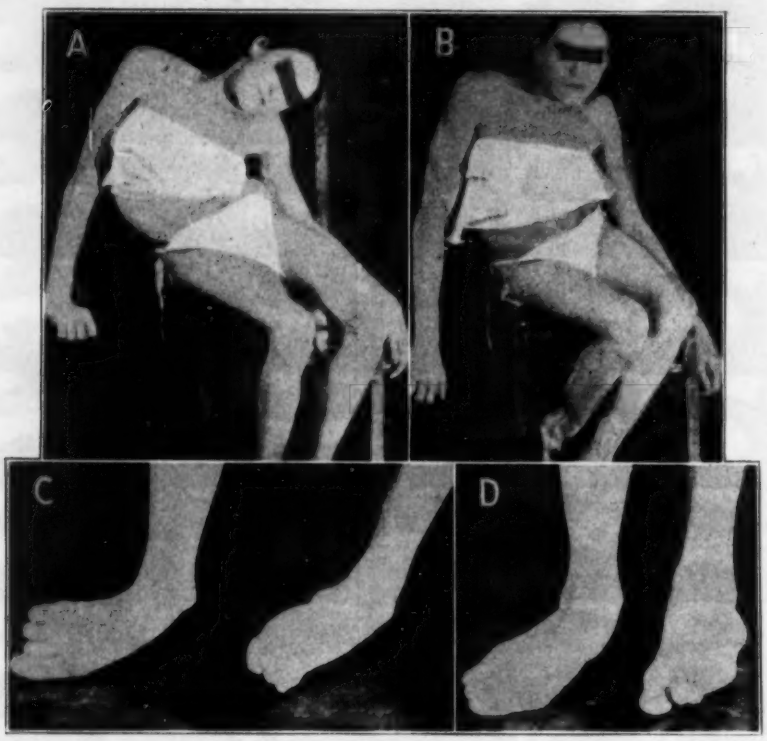

Fig. 4 (case 2).—*A*, patient sitting on chair; *B*, patient in more upright posture; *C*, feet in extreme supination; *D*, left foot relaxed.

Mental and laboratory examinations revealed nothing abnormal.

The question of operation was discussed with the patient, but she stated that her symptoms were not sufficiently severe or incapacitating to justify surgical procedure.

Film Analysis.—The patient was sitting on a chair. The upper part of the trunk was bent far to the left so that the chest and the pelvic portion formed almost a right angle (fig. 4 *A*). The head and both arms were held in a natural position. The right thigh was adducted; the left foot was kept in extreme supination, and the right foot was held in extreme pronation and lateral flexion.

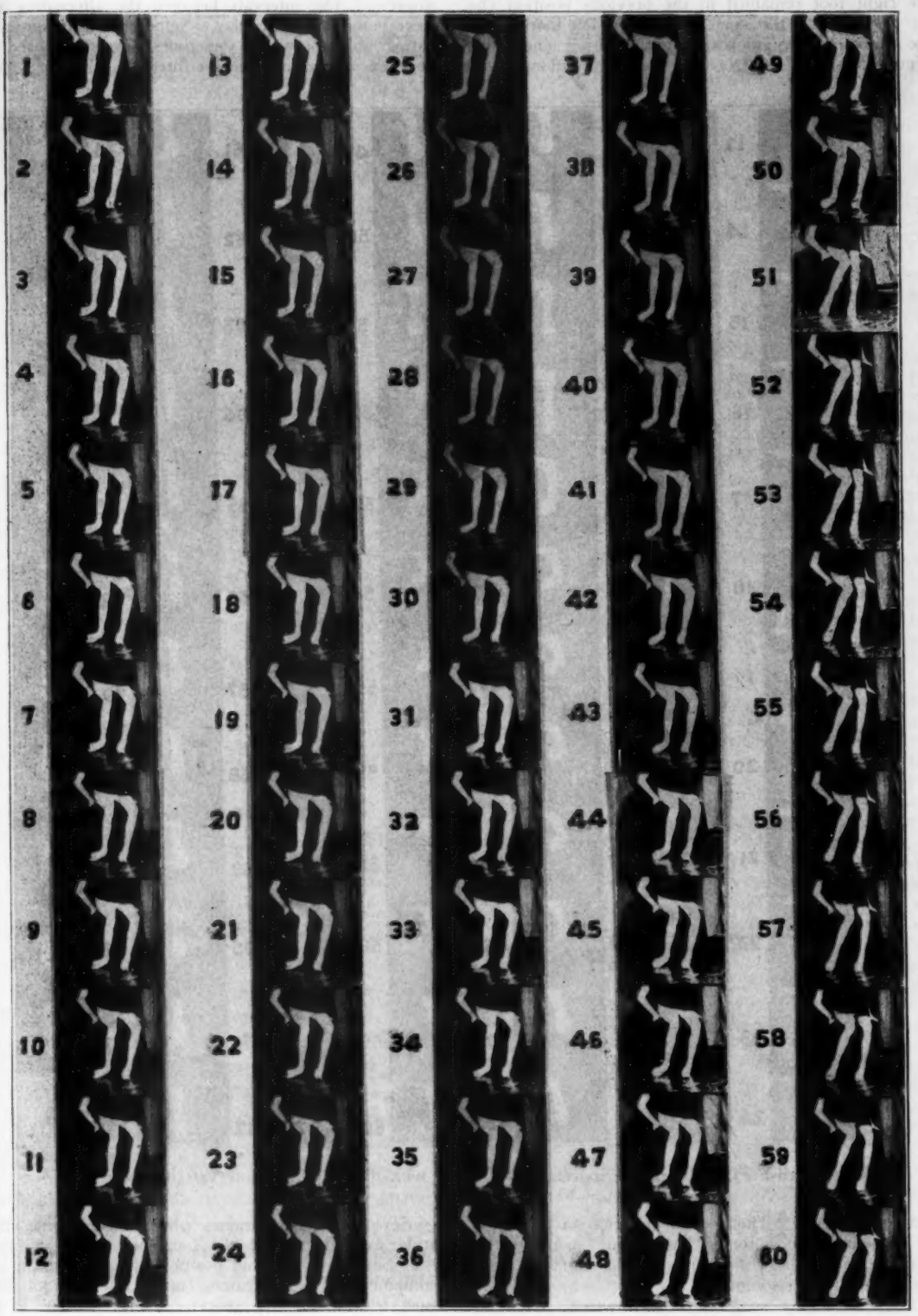

Fig. 5 (case 2).—Posture of right foot, maintained for a long time, with sudden change between frame *50* and frame *51*, that is, in one-sixteenth second.

After a while the tension in the left foot relaxed, and the foot returned to a middle position; meanwhile, the right foot remained in the previous position (fig. 4 *C* and *D*). At the same time, as the left foot relaxed the trunk took a more upright position (fig. 4 *B*). Figure 5 shows a series in which pronation of the movements of the right hand appeared (dorsal and volar flexion, with slight flexion and extension of the fingers). The intervals between the alternating units were completely irregular. Sometimes only one alternating unit appeared; sometimes bursts of three, five or more, always at different intervals. Figure 6 shows

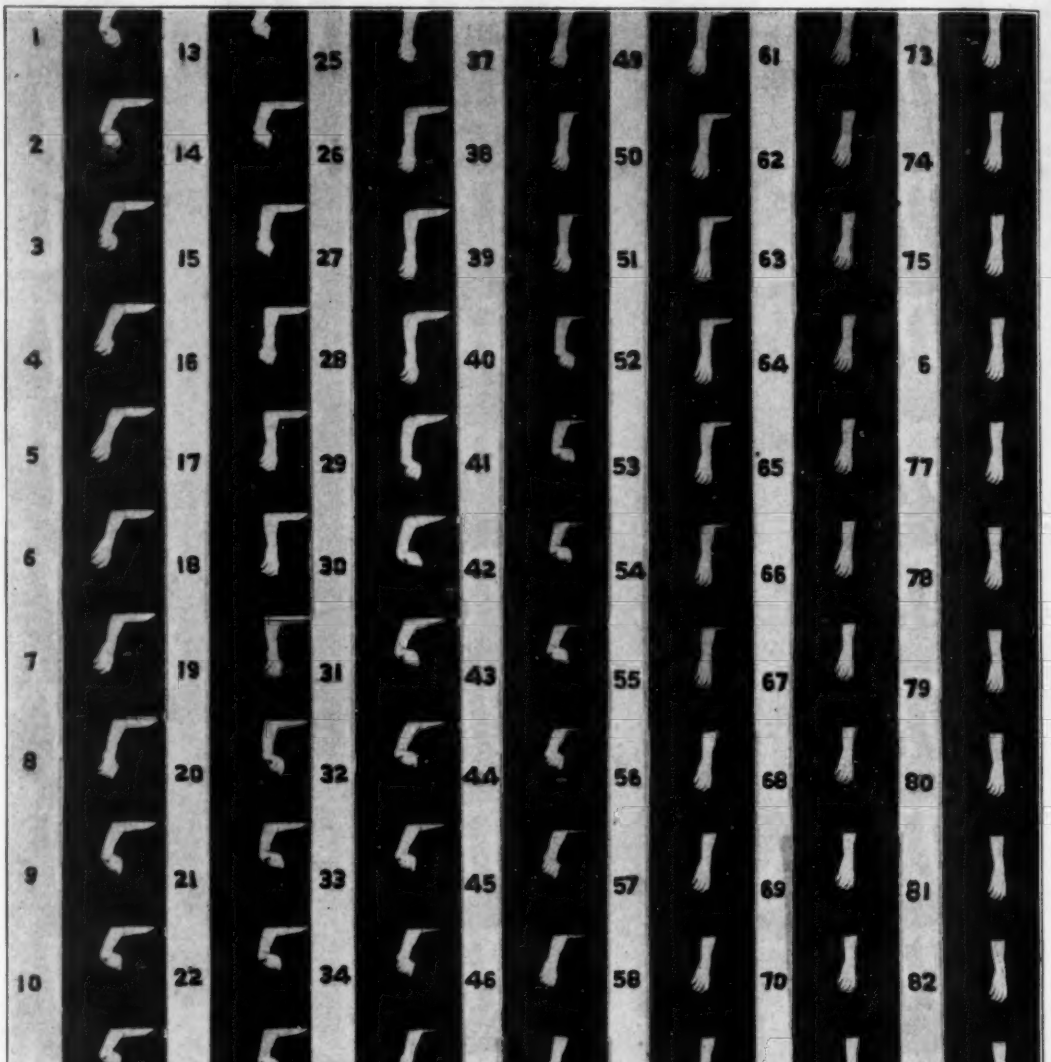

Fig. 6 (case 2).—Alternating movements of hand, with different time intervals between them.

right foot relaxed. The peculiar position of the right foot was maintained for a long time; suddenly the position changed, between frame *50* and frame *51*, that is, in one-sixteenth second.

Then involuntary movements of the right arm and hand started, and transient adductions of both thighs occurred. Later the patient is shown sitting, with still more pronounced scoliosis.

A close-up view of the right arm and hand revealed that after a long period of complete rest, alternating a series of successive frames which illustrate the alternating movements and the long periods of complete rest. Sometimes the end position of an extension was maintained for a few frames before a flexion followed. Much less involuntary movement was present in the left hand.

A close-up view of the legs and feet revealed slow adductions of the thighs at irregular intervals, those on the two sides being independent of each other. The long-maintained positions of the feet were most pronounced,

the right foot being in pronation and the left in supination. This seemed to be a position of predilection of the feet; it disappeared and appeared again (fig. 4*C*).

A close-up exposure of the head and neck showed slow contractions of the right sternocleidomastoid muscle and of the pectoral muscles, more on the right side than on the left. The head was usually bent to the left.

When the patient was standing, the kyphosis of the trunk was much less pronounced. There were abundant involuntary movements of the right hand of the same character as those already described. In walking there were extreme kyphosis and lordosis of the spine, and the whole trunk was bent forward at the hips. The left leg was more flexed at the hip than the right leg, and the left foot was in extreme plantar flexion, so that only the toes touched the floor in walking. Before the patient started to take the first step she had both soles on the floor. At the moment she lifted the left leg out, the persistent plantar flexion of the foot appeared.

A finger to nose test showed no ataxia. There was no motor disturbance in either arm when she drank a cup of water. As she lit a match some involuntary movements of the right arm appeared, but did not interfere with the act.

In passive movements both arms and hands appeared hypotonic. In passive movements of the head the sustained contractions of the right sternocleidomastoid muscle sometimes stopped the movement.

There was no history of a birth injury, and the patient's early development was normal up to the age of 8 years, when motor disturbances began. On her first and second admissions to the hospital this condition was described as deformity and rigidity, of variable intensity and degree, with dystonic tensions maintained for longer and shorter periods. The course of the disorder was steadily progressive. After the disease had been present about twelve years, the postural disorder was extreme. Some positions were maintained permanently during observation, but suddenly appearing changes and relaxation of the affected part gave evidence that sustained tensions were responsible for their appearance. More transient dystonic movements, at completely irregular intervals, appeared in the neck, the shoulder girdle and the extremities. In addition, more rapid alternating movements, with the characteristics of myorhythmia, particularly of the right arm and hand, appeared between them.

The resistance to passive movements seemed to be diminished when involuntary motor activity was not present. Only when tensions appeared in the part under examination did sudden obstruction hamper the passive movement and give the impression of increased resistance to such movements. This phenomenon has been described as alternation of hypotonia and hypertonia. But the basic condition of the muscle and its reactions to passive movements are not changed. Only the suddenly appearing sustained tensions interfere with the continuous course of the passive movement.

Except for the involuntary movements and postures, the neurologic examination did not reveal any disturbance. The outstanding clinical feature of this progressive disease is the elective systemic appearance of dystonic disorders in a healthy child. No etiologic factor could be determined.

CASE 3.—*History.*—E. S., a man aged 34, entered the hospital in 1938.

His birth was normal, as was his early development. He started to walk and talk at the normal age and entered school before the average age. He was well until the age of 12 years, when a disturbance in his right hand developed gradually. "I could not propel the pencil across the page; it seemed to me I had not enough power to guide the pencil. I had to lift my arm in the shoulder, and then this feeling disappeared." This symptom was followed soon by irregular alternating movements of the entire right arm, which occurred only when the arm was kept extended. In 1918, during the influenza epidemic (when he was 14 years old), he had a severe illness of about two weeks' duration. After his recovery he noticed irregular movements and incoordination when walking. At this time he could run much more perfectly than he could walk at a slow pace. At the age of 16 he first noticed the occurrence of involuntary movements of both legs when he had to sit quietly in a narrow seat. Although he could walk for a certain distance without much trouble, something suddenly would "click," and he would lose his coordination. At the age of 20 the incoordination of the legs became generally worse; he was weak and had to interrupt his college work for a year to rest on a farm. After his return to town his condition again grew worse, but he was able to continue college work, with interruptions. He acquired a teaching position and held it until 1935, when involuntary movements began to occur in his right shoulder and his back; these gradually became worse during the following two years. At this time tensions became more pronounced; there was stiffening of the muscles, and it was difficult to relax unless he lay down and rested his head against a solid support. He stated: "The tenseness was maintained for long periods and grew worse as the day went on. At night the tension was completely reduced only when I had been in bed for some time. Sometimes it took a few hours before I could relax sufficiently for sleep. During sleep all muscles were relaxed." His balance had been poor since the spring of 1937, and he had had to give up his activities. He was treated during this period with all kinds of drugs and with physical therapy and sedation, without more than transient relief.

The family history is noncontributory.

Examination.—Neurologic examination showed nothing abnormal except for the abnormal involuntary movements and the features to be described in the film analysis.

Operation.—Dr. Tracy Putnam performed an operation in September 1938. The anterior roots of the first to the third cervical segment were coagulated and crushed on each side. The spinal accessory nerve was similarly treated within the foramen magnum, and the anterior column of the cord was cut between the second and third segment on the right side.

Since the operation the patient has resumed his teaching and has felt much better. It is his subjective impression that only his "tensions," particularly those in the shoulders and neck, have been benefited, and that his involuntary movements have not been improved to the same extent.

Film Analysis.—Preoperative Pictures: When the patient was sitting (fig. 7 *A*), the head was bent far to the right and turned to the left. The right shoulder was drawn up, and the upper portion of the right arm was abducted. The trunk was twisted to the left.

When he started to raise his arms to the horizontal position, both shoulders (the right more than the left) were drawn up, and the head was bent farther to the right. While the arms were held in the horizontal position, there were irregular, slow involuntary movements of the upper part of the arm and alternating movements of the right arm and hand. The trunk was more twisted and was bent far to the left, and the head was drawn to the left.

While he was walking, tensions of the right leg, the shoulder girdle and the trunk and wide balancing movements of the right arm appeared. These sudden tensions made the gait resemble jumping.

Postoperative Pictures (May 26, 1941): With the patient standing (fig. 7 *D* and *E*), the head was held slightly bent to the right and turned to the left. The trunk was bent to the left. The right shoulder was held higher than the left. He stood with the legs apart. The right leg was completely extended. There were some turning movements of the head. The right leg was inverted and was kept in this position for a long time. After he had stood longer, the bending of the trunk increased, and the trunk turned more to the left (fig. 7 *E*).

In his walking there was some instability; the right leg was held stiff for a few steps and then lifted from the ground in wide circumductions. Suddenly the bending of the trunk increased, and sustained tensions appeared in the muscles of the neck, shoulders and back. Transient tensions bent the upper part of the body forward or to the left. There was an almost continuous overflow of balancing movements of the right arm.

When he was in the sitting position, the trunk was held fairly straight (fig. 7 *C*). There were slow, sustained movements of the muscles of the shoulder girdle and the pectoral muscles. As soon as he raised both arms to the horizontal position, the curvature of the spine to the left increased, and the right shoulder was higher than the left. Irregular movements of the right arm and hand appeared, part of them of alternating type.

When the patient drank a cup of water held in the right hand, involuntary movements appeared in greater number in the right arm and shoulder. The shoulder was drawn farthur up and was kept in this position for a time. The head was bent to the right. There were sustained tensions of the muscles of the shoulder and the pectoral muscle and alternating movements of the right arm and hand. When he drank with the cup in the left hand, involuntary movements appeared almost exclusively on the right side.

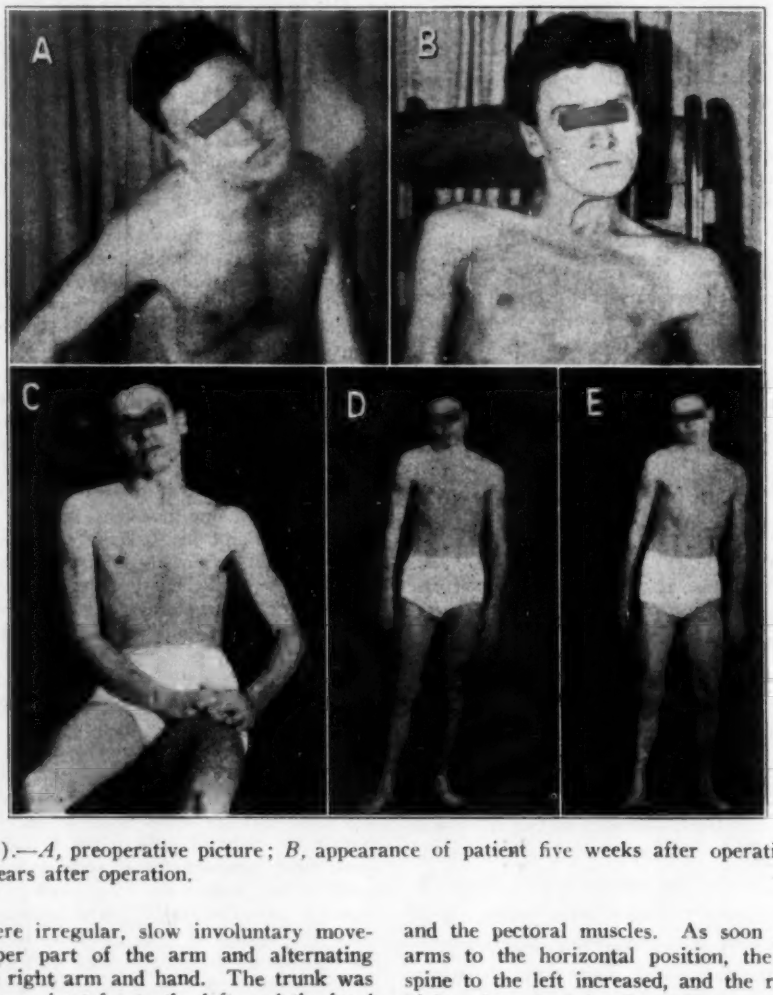

Fig. 7 (case 3).—*A*, preoperative picture; *B*, appearance of patient five weeks after operation; *C*, *D* and *E*, appearance two years after operation.

Writing at the blackboard with the left hand was interfered with only by tensions in the shoulder girdle. Writing with the right hand produced severe hyperkinesis: alternating movements of the forearm and hand. Sustained tensions of the whole arm sometimes stopped the act of writing. Not infrequently excessive pressure was exerted. Slow motion pictures showed clearly how the disturbances of writing were brought on.

The first symptoms developed in a normal child at the age of 12 years. Delivery and early development were without disturbance. The patient was intelligent and gave an instructive description of his symptoms, differentiating "tensions" (he used this expression spontaneously) from involuntary movements. "Tensions" were described as a feeling of stiffness in one muscle or in a muscle group which did not always lead to a movement of a limb. Sometimes it was only a "funny feeling," which came on without a recognizable reason. Sometimes he recognized that he could not carry out a voluntary act because he could not relax one part in order to move it in another direction.

The disorder started in the right arm and hand and gradually progressed to the trunk, the neck and all four extremities. During sleep all muscles were relaxed, but it took some time for complete relaxation when he was lying in bed.

The site and degree of the sustained motor activity which brought on the dystonic postures changed continuously. *D* and *E* of figure 7 show postures taken after a short interval. Analysis of the movements during this period reveals that between the first and the second position the twisting of the trunk had increased and the position of the right foot had changed considerably. Dystonic movements, not maintained nearly as long as dystonic postures, were observed in the neck, trunk, shoulder muscles and lower extremities, sometimes disturbing the equilibrium while the patient was standing or sitting. The upper extremities showed, in addition, alternating movements at irregular intervals, previously described as myorhythmia.

When voluntary movements or acts were performed, the involuntary motor activity was much increased. When the patient was walking, drinking or writing, dystonic movements and tensions appeared in greater number, and the change in posture was more extensive than when he was lying down or sitting in a relaxed position with the head and arms supported. Under these conditions the involuntary motor activity appeared as associated movements released under the influence of voluntary motor acts.

Aside from the dystonic motor disturbances, neurologic examination revealed nothing abnormal. The illness during the epidemic of influenza of 1918 came on a long time after the onset of the motor disorder and is not of etiologic importance. One is entitled to include this case with the dystonias of unknown cause which present elective systemic symptoms and have their onset during childhood.

Comparison of *A* (fig. 7), taken before operation, with *B*, taken five weeks after operation, and *C*, taken two years after operation, demonstrates the success of the anterolateral chordotomy. The patient himself offered the observation that the improvement in the tension and the feeling of stiffness was definitely a result of the operation. The posture was much more relaxed. Although some sustained contractions appeared after operation, their extent and severity were reduced. During voluntary activity there was still some involuntary stiffening, but it did not hamper his voluntary activity as much as before operation.

CASE 4.—*History.*—N. Z., a white man aged 26, was born in Poland. There was no history of birth trauma or of familial disease. He developed properly and was in fairly good health. An attack of "sleeping sickness," at the age of 4 years, of about a month's duration, was reported, but detailed data could not be obtained.

At about 13 years of age he began to have almost constant involuntary movements of the right arm and hand. Although he was right handed, he began to use his left hand in writing. In May 1938 the patient experienced a moderate amount of dull pain in the lower lumbar region, which lasted for two days. After this he began to have involuntary movements of the muscles of the back and neck which entirely distorted his normal erect posture. He had great difficulty in walking until about a year prior to admission, when he was placed under treatment with Bulgarian belladonna root. On occasions, for about two hours after a dose of this drug, he had only slight involuntary movements.

Physical Examination.—Inspection revealed good development. There were kyphosis and scoliosis of the thoracic region, with the concavity to the right. Sustained posturing of the head, the right shoulder and the spine, with involuntary movements in the right upper extremity, was noted. Muscular strength was good on both sides; there was no atrophy. Speech was normal. The reflexes were active and equal on the two sides. The Babinski response was not elicited. Sensory examination gave normal results. The patient was cheerful, cooperative and of adequate intelligence.

Laboratory tests gave normal results. The electroencephalographic record was normal. Hyperventilation did not elicit any abnormalities.

Operation.—Laminectomy was performed, and the anterior surface of the right side of the cord, between the second and the third cervical segment, was cauterized. The patient had remarkable relief immediately after operation, but improvement decreased in the succeeding weeks.

Film Analysis.—When the patient was standing, there was only slight lordosis of the spine, and the upper part of the body was slightly bent and turned to the left. The head was held upright. After a while the chest became bent forward to an extreme degree, and the head drooped (fig. 8 *A* and *B*). With the extreme lordosis, there was increased twisting of the trunk. The

Fig. 8 (case 4).—*A* and *B*, chest bent forward and head drooping; *C*, sustained contraction of superficial and deep muscles of neck; *D*, twisting and bending of trunk as both arms are lifted to horizontal position.

right shoulder drooped. This posture was maintained for a while; then the patient returned to the upright position. During the twisting of the trunk involuntary movements of the neck, shoulders and both arms occurred. A close-up series of the right arm showed sustained tensions, resulting in adduction and extension at the elbow, which was maintained for a while.

When the patient lifted both arms to the horizontal position (fig. 8 *D*) bending and twisting of the trunk were produced, so that he was forced to balance the position of the right arm continuously.

A close-up picture of the neck and shoulders showed irregular contractions of the muscles of the upper portions of the arms and the shoulder blades and the deep and superficial muscles of the neck. The contractions were long sustained and appeared and disappeared at irregular intervals. Sometimes the contractions of the trapezius and sternocleidomastoid muscles (fig. 8 *C*) were maintained for a few seconds. The right side of the neck and the right shoulder appeared to be more affected than the left.

Two series of motion pictures, taken four weeks and six months, respectively, after operation, revealed no change in the original position, and appearance of alterations in position and tensions was the same as before. When the patient brought the arms to the horizontal position there was, again, increase in bending and twisting of the trunk, with balancing movements, particularly of the right arm. Sustained movements of the muscles of the neck and shoulders were visible.

A boy with a history of normal delivery and development was reported to have had an attack of "sleeping sickness" at the age of 4 years. It seems doubtful whether he suffered from epidemic encephalitis at this time, for, he did not show any residuals of the disease in the following years and was healthy until the age of 13, when involuntary movements of the right arm began. Further progression occurred at the age of 24, when sustained tensions started in the muscles of the neck and back. At the age of 26 dystonic movements of the deep and superficial muscles of the neck were present, but particularly remarkable was the distribution of tensions which caused the peculiar posture. The upper part of the spine was bent forward, and the head drooped. This postural disorder predominantly occurred as an associated movement brought on by other motor activity, such as standing for a longer period or raising the arms to the horizontal position.

In addition, there were some alternating movements of the right arm, which also appeared as associated movements with voluntary movements of the upper extremities.

No other abnormalities were revealed by the neurologic examination. Specifically, oculomotor symptoms, rigidity, tremor and other possible evidence of chronic epidemic encephalitis were not noted.

Clinical observation and examination revealed only a progressive disease, without evident cause but with elective systemic symptoms, consisting of dystonic movements and posture.

The surgical procedure (anterolateral chordotomy) was without effect on the involuntary motor activity.

Case 5.—R. A., a man aged 22, was referred to the Neurological Institute for possible operation to correct his involuntary movements, which involved all four extremities, the head and the neck. His delivery had been completed by forceps. He had been rather slow in general development. His teeth appeared at the age of 2 years; he did not begin to sit up until he was 4 and did not walk until he was 7 years of age. At the age of 10 years involuntary movements of the right lower extremity were noted. Shortly thereafter all four extremities were somewhat involved. These involuntary movements gradually progressed and reached their greatest development at about the age of 15. Since that time his condition has remained static.

The family history was noncontributory.

Physical Examination.—The patient was able to walk and seldom fell. Muscular strength was generally good, with no apparent difference on the two sides. Speech was slow, explosive and slurred. The deep tendon, abdominal and cremasteric reflexes were present and equal on the two sides. No pathologic reflexes were elicited.

Sensation and the cranial nerves were normal.

Psychometric examination revealed low average intelligence, with an intelligence quotient of 77.

Laboratory examinations revealed nothing of significance.

As the boy seemed to be fairly well adjusted, Dr. Putnam felt it was inadvisable to perform an operation, lest weakness be produced on one side and the patient further incapacitated.

Film Analysis.—When the patient was standing (fig. 9 *A*), the head was tilted and turned a little to the left. The trunk was also turned to the left. The left arm was held slightly abducted at the shoulder and bent at the elbow. The right arm hung down in a natural, relaxed position. The legs were held apart, and the left leg was slightly adducted and inverted. The right sternocleidomastoid muscle was in constant, clearly visible contraction (fig. 9 *B*). There were slow turning movements of the head to the right. Both arms swung around to the back, and at the same time there were irregular alternating movements of the upper part of the arm and the forearm. These movements were sometimes arrested by sustained tensions.

When the patient spoke, the turning movements of the head increased in number, and slow movements of the shoulder girdle appeared, with adduction of both arms.

There were little hyperkinesis of the face and only a few movements of the hands and fingers. The hands showed only movements associated with movements of the entire arm.

The finger to nose test revealed no ataxia but brought on an increase in torsions of the trunk and head to the left.

When he was walking, increase in torsions of the trunk and head and in the involuntary movements of the arms was evident, but the gait was most interfered with by long-sustained extension and adduction of the left leg. The leg swung around like a stick, and the knee was not flexed (fig. 9 *C*). The foot did not drop but was held in a natural position.

After the patient's birth by forceps, gross disturbances were not noticed, but his general physical development was remarkably slow and mental development progressed only to that of low average intelligence. The intelligence quotient at the age of 22 was only 77.

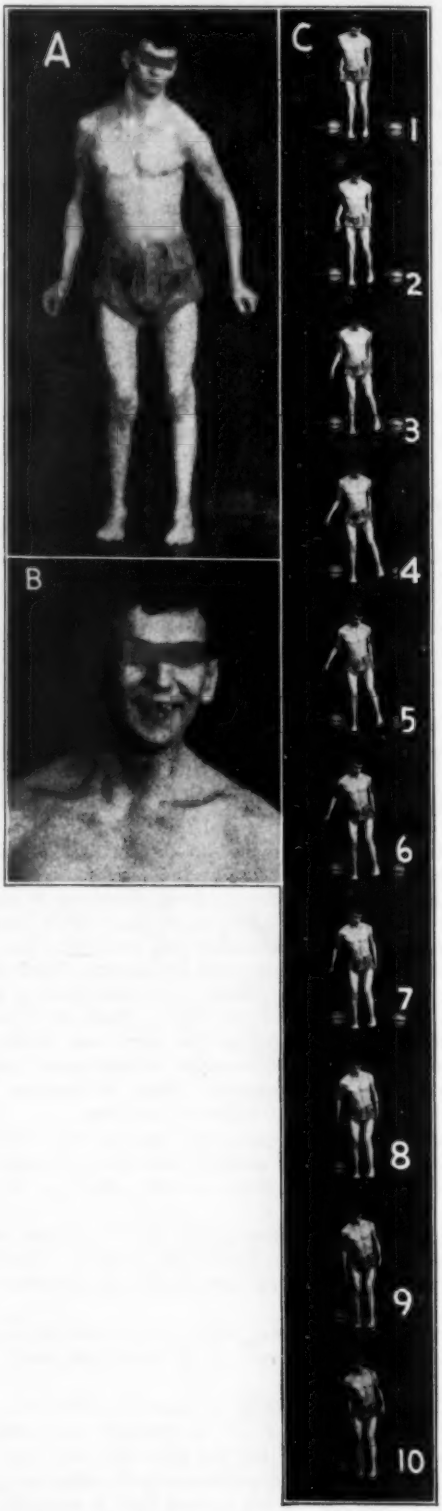

Fig. 9 (case 5).—*A* and *B*, dystonic posture; *C*, swinging around of leg in walking.

Involuntary movements started at the age of 10 years. They first affected the right lower extremity only, but progressed quickly to the trunk, the neck and all four extremities. Speech seemed to be somewhat affected also. The abnormal involuntary motor activity consisted of slow dystonic movements. They came on at different intervals in different parts of the body in continuously varying pattern and then disappeared. Their occurrence interfered with voluntary action. Maintained postures or permanent distortions were not observed. Sudden extension of the leg caused disturbance in walking. Neurologic examination revealed no other abnormalities. Dystonic motor disorders were, again, the only elective symptom of this disease.

There was no history that a birth injury had caused a localized gross lesion in the brain. But the slow physical development and the reduction in mental growth lead to the presumption of the presence of a malformation of the brain at birth. The disease, which started at the age of 10 years, developed in an already abnormal nervous system. Whether the same process caused the developmental retardation and, after a latent interval of at least ten years, the progressive hyperkinesis, or whether a progressive process appeared at the age of 10 in a malformed brain, cannot be decided from clinical observation alone.

Case 6.—*History.*—K. G., a single woman, entered the hospital at the age of 28. The family and the past histories were essentially noncontributory. When she was 12 years old, she noticed that her writing became unsteady and that she had difficulty in controlling the movements of her right hand. This difficulty existed for one year; she was then free from it for three years. In her third year in high school the trouble returned. It became so extreme that she was unable to hold a teacup, knife or fork. Later involuntary movements appeared, and her right arm and hand would twist and turn even when she was at rest. In 1936 the same difficulty gradually developed in her left hand. In 1941 she noticed that her head moved spontaneously and that she was unable to control its motion. Shortly thereafter a feeling of tightness developed in the back of her neck, and her head began to pull to the left. This condition persisted until her admission to the hospital, in February 1942.

Examination.—Physical examination revealed no pathologic condition of the inner organs. The heart and lungs were normal; the blood pressure was 110 systolic and 80 diastolic. Neurologic examination showed no weakness of the extremities. The tendon and the abdominal reflexes were equal and active on the two sides. No pathologic reflexes were elicited. Sensory examination gave normal results, and there was no abnormality of the cranial nerves.

The report of the psychologic examination was as follows: "The patient is a young woman of high average intelligence. She does better work with verbal material,

as one would expect in view of her difficulty in the use of her hands."

Roentgenograms of the skull revealed nothing abnormal.

Operation.—Operation was performed by Dr. Putnam on two occasions. At the first operation a laminectomy was performed, and the anterior roots of the first, second and third cervical spinal segments, together with the spinal accessory nerve, were crushed and cauterized bilaterally. After operation the patient felt much more relaxed, but there was still tension of the left sternocleidomastoid muscle, which produced tilting of the head to the right. On the twenty-fourth postoperative day the left spinal accessory nerve was sectioned at the neck. After this operation the head could be held in good alinement, and there was no palpable abnormal tension of the muscles of the neck. Movements of the muscles of the arm were of the same type as before operation.

Film Analysis.—When the patient was standing the head was bent slightly to the left and turned far to the right. The trunk was bent to the right, and the left shoulder stood higher than the right. Both arms hung down and were in extreme pronation, so that the palms faced outward (fig. 10 *A* and *C*). There were turning movements of the head and involuntary movements of both hands and the fingers. The spine showed lordosis and kyphosis of variable intensity, the concavity being turned to the right.

A close-up view of the upper part of the body showed intermittent, long-sustained contractions of the left sternocleidomastoid muscle and some contractions of the shoulder and the pectoral muscles, more pronounced on the left side than on the right (fig. 10 *B*).

A close-up view showed two kinds of involuntary movements of the hands and fingers: (1) slow movements at irregular intervals with a continuously changing pattern, consisting in dorsiflexion of the hand with extension of one finger, flexion of the thumb and another finger, radial or ulnar flexion of the whole hand and extension of the thumb, and (2) alternating movements of the hands and fingers, consisting in dorsiflexion and volar flexion of the whole hand, extension and flexion of some of the fingers, and pronation and supination of the forearm and hand. The intervals between these antagonistic units were irregular. The pattern changed frequently: Flexion and extension of the fingers were followed by pronation and supination of the hand; then radial and ulnar flexion of the hand was carried out a few times. As these two kinds of movements were intimately mingled, the pattern of hyperkinesis was complicated.

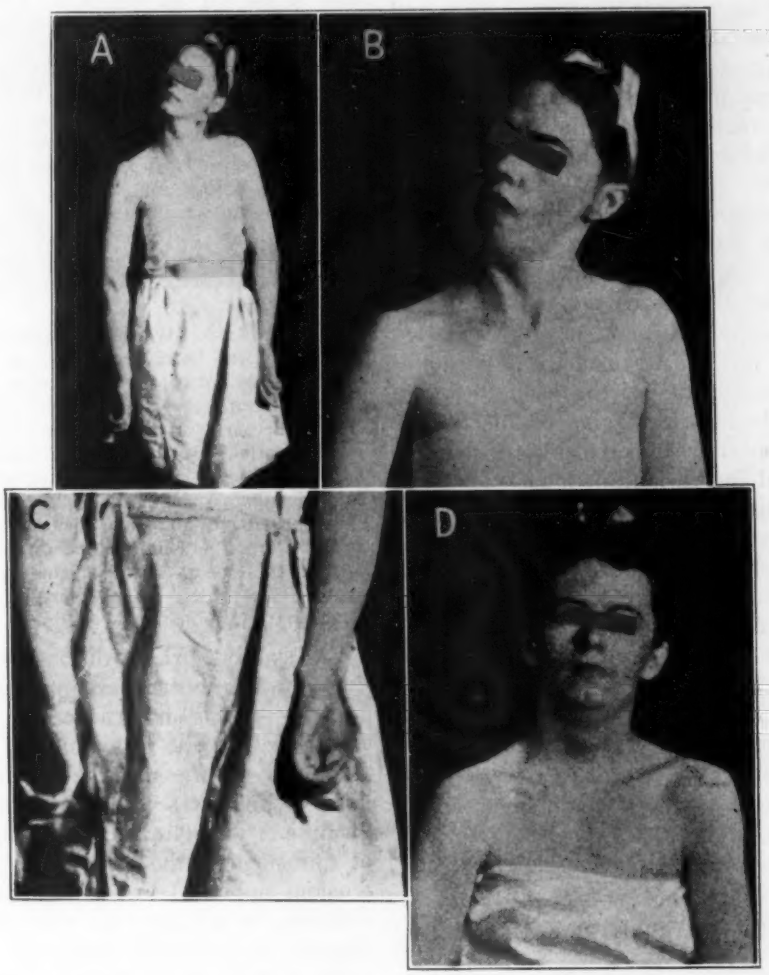

Fig. 10 (case 6).—*A*, *B* and *C*, preoperative pictures; *D*, postoperative picture.

In walking the patient exhibited increased turning movements of the head, and the spine appeared much more bent than when she was standing. Both arms presented the usual number of associated movements.

After operation only the position of the head was improved (fig. 10 *D*). The head was held straight; the position of other parts of the body was unchanged. There were the same involuntary movements of the shoulder girdle, hands and fingers.

After normal delivery and normal development, the patient first showed motor disorder of the right arm and right hand at the age of 12 years. The movements were not severe and interfered only with the act of writing. After apparently complete recovery for about three years, involuntary motor activity recurred in the right upper extremity. Now the disorder was steadily progressive, and twitching and turning movements of the right arm appeared. Further progression was noticed at the age of 23, when both arms, and the neck and the trunk were affected. The face and the lower extremities never showed any involuntary motor disturbance.

At the time of observation, the most troublesome symptom was the torticollis. Besides the slow turning movements of the head, dystonic movements of the muscles of the shoulder girdle and the back appeared at irregular intervals and were maintained for various periods. Tensions of longer duration caused peculiar postures of the head (torticollis), the upper extremities and the trunk (kyphosis and lordosis). In both hands slow, athetotic, irregular movements of the fingers were intermingled with alternating movements, described previously as myorhythmia. In walking both types of involuntary activity, the dystonic symptoms and the alternating movements, were increased in intensity.

The operation was successful in relieving the torticollis. The head was maintained in a straight position, and the sustained contractions of the left sternocleidomastoid muscle were considerably decreased.

The neurologic examination did not show any abnormality except for the dystonic symptoms. Here, again, is a case with elective appearance of dystonic symptoms without a recognizable cause. Although the first symptoms appeared at the age of 12 years, the real progress of the disease began several years later. The progress was not as rapid as that when the disease had an earlier onset.

CASE 7.—*History.*—A. K., a woman aged 32, was born in New York, of Russian Jewish stock. There was no apparent hereditary tendency in the family. Delivery was normal, and her weight at birth was 12½ pounds (5,670 Gm.). Development was normal, without any disturbance. After leaving high school, at the age of 16, she worked as a stenographer. She was well up to the age of 18. At this time she noticed slight dragging of the left leg when she walked. During the first few years, in which she had this feeling alone, even physicians could see nothing peculiar in her walk. The region of the left hip and thigh was affected; in addition, she later felt "a sort of strain" in the left knee. In 1930, at the age of 24, she had increased difficulty in walking. She stated: "At this time it seemed to change the posture; I began to twist and turn in the hip, but only in walking." In addition, her handwriting became poor. In writing she felt a "tension" in the right forearm, which became more pronounced in the year preceding admission to the hospital.

At the time of admission she complained only of tension in the left leg and in the left side of the back when she was walking. Some tremor appeared in the left leg when it was under strain, e. g., when she put weight on it. In walking the foot turned inward at irregular intervals. It tired her to make the movements of walking, and she used the right leg more than the left. This difference was pronounced when she kept her arms together or when she carried packages in her arms. "It seems to lock my left leg, and I can't operate it without balancing; this is due also to the tensions in the back." She had no other physical complaint.

Physical and neurologic examinations did not reveal anything abnormal except for the motor disorder, to be described later.

Film Analysis.—When the patient stood or sat, the position of the head, trunk and upper and lower extremities was not changed. No lordosis or kyphosis was noted. When she walked, and still more when she crossed her arms over her chest in walking, slow outward rotations of the left leg appeared at irregular intervals. At the same time, contractions of the muscles of the left lower part of the back appeared, which caused slight bending of the spine to the left.

In slow motion pictures the differences between the regular movements of the right leg and the slightly distorted movements of the left leg in walking were clearly recognizable.

A healthy girl, with a history of normal delivery and normal development, had a gradual onset of motor disturbances at the age of 18 years. When she was walking, she noticed the feeling of tightness in the left lower extremity. The feeling was only subjective; numerous examiners failed to recognize any motor defect at this stage of the disease. At the age of 24, tensions appeared in the right arm and caused difficulty in writing; she then exhibited visible changes of posture in walking.

Up to the age of 36, when the patient came to the Neurological Institute, there was only slight progression of the disease. When she was standing or sitting, no involuntary movements or changes of posture could be noticed. When she was walking, turning movements of the left leg and twisting of the lumbar part of the spine came on as associated movements at irregular intervals.

During the whole course of the disease these dystonic symptoms were always the only objective sign. Neurologic examination revealed no other abnormality. No etiologic factors could be identified.

The coincidence of the late onset of the first symptoms and the slow progression and circumscribed distribution of the disorder is remarkable.

Case 8.—*History.*—J. F., a man aged 31, complained chiefly of torticollis, which pulled the head to the right and had been present about eight years. It began as stiffness of the left sternocleidomastoid muscle and gradually emerged into a spasm, during which the head was drawn to the right. During the first year after the onset of symptoms there was gradual progression of the disease; afterward the condition became fairly well stabilized. In fact, since 1932 the jerking of the head had been practically constant. The condition became worse when the patient was tired and improved with rest. Emotional upsets accentuated the disorder. Soon after the development of the torticollis it was noticed that the patient had a curvature of the dorsal portion of the spine, with the convexity to the right, and that this produced a prominence of the right side of the chest. Movements occasionally occurred in the muscles of the back.

The past history revealed that the patient had "rheumatism" at the age of 13 years, which affected the ankles and knees but left no sequelae. He had had no other serious illness.

Examination.—The patient was tall and well developed, with dorsal scoliosis and pronounced torticollis. The results of neurologic examination were normal except that the reflexes were slightly greater on the right side than on the left.

Operation.—Laminectomy and section of the motor roots of the second and third cervical nerves and the roots of the spinal portion of the left accessory nerve were performed by Dr. Putnam.

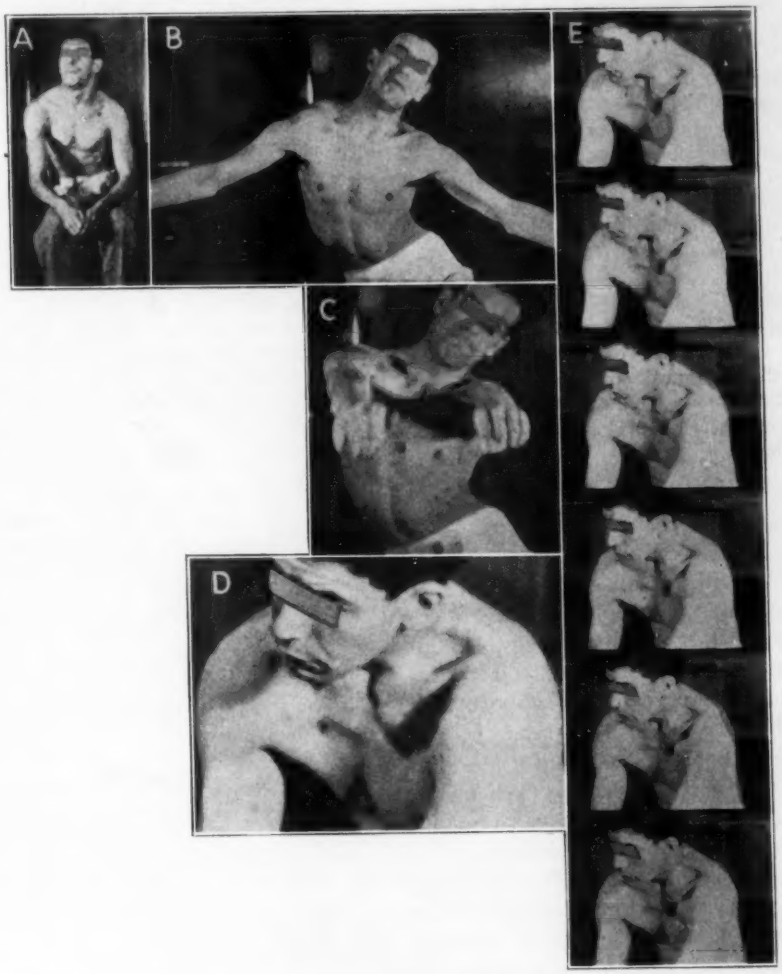

Fig. 11 (case 8).—*A*, patient sitting; *B*, change in posture produced by patient's raising the arm; *C*, similar change produced by patient's turning around, with his hands outstretched in front; *D* and *E*, maintained contraction of left platysma and pectoralis muscles.

Film Analysis.—Moving pictures were not taken before operation. The first part of the film was taken eighteen days after operation.

When the patient was sitting comfortably on a chair (fig. 11 *A*), the head was slightly bent to the right and twisted with the chin to the left. The left shoulder was kept a little lower than the right. There was slight curving of the trunk, with the concavity to the left.

Voluntary elevation of the arms to the horizontal position (fig. 11 *B*) was accompanied by change in the posture of the head and trunk. The head was extended and turned farther to the left; the curvature of the

trunk was much increased. This posture was maintained as long as the arms were kept raised. After the patient lowered his arms, he assumed his original position. When he stood upright, he kept his head turned farther to the left than when he was in the sitting position. The curvature of the trunk was almost the same in the two positions. This change in posture appeared again as the patient was turning around and as he kept his hands outstretched in front (fig. 11 *C*).

In the second part of the film, taken four months after operation, the posture was not much changed except that the left shoulder drooped more. A close-up view of the head and chest (fig. 11 *D*) showed sustained tensions in the platysma muscle and in both pectoral muscles (more on the right side than on the left). At irregular intervals the muscles on the two sides contracted in complete independence of one another, and the contractions were maintained for quite different periods (fig. 11 *E*). During some contractions the head was drawn to the left; sometimes only the pectoral muscles contracted, without the head's being affected.

Contractions of Left Pectoral Muscle: Contractions appeared in two frames, were sustained in nine frames and disappeared in one or two frames. Again, they appeared in two frames, were sustained in thirty-seven frames and disappeared in two frames. After an interval of six frames, a new contraction appeared in two frames and was sustained for one hundred and five frames. During this sustained contraction of the left pectoral muscle, shorter contractions of the left platysma, the left trapezius and the right pectoral muscle appeared and again disappeared.

In a man who had never been ill before, dystonic contractions of the left sternocleidomastoid muscle appeared at the age of 23. Nothing is known of any disturbances during delivery or in his later development. No infectious disease or other condition could be considered as an etiologic factor. Physical examination did not reveal any abnormality except the involuntary motor activity.

There was only slight progression of the disease. At the time of observation, when the patient was 31, the sustained turning movements of the head were still present; in addition, contractions of the pectoral muscles were long sustained, and contraction of the muscles on one side of the back produced changes of posture. These postural disorders came on spontaneously but appeared more regularly when the patient made voluntary movements with his arms or was walking.

The predominant symptom in this case was the torticollis, but in the progression of the disorder from the muscles of the neck to the pectoral muscles and the muscles of the back the condition resembles the picture in cases of the dystonia group. The combination of late onset with slow progression and circumscribed distribution of systemic motor symptoms is notable.

The patient felt subjectively better after the operation and has returned to work.

CASE 9.—*History.*—P. W., a white boy aged 9 years, entered the hospital for an anterolateral chordotomy.

The history revealed that the mother's pregnancy was normal and that after a precipitate delivery, the infant was cyanotic and required artificial respiration. His weight at birth was 4 pounds 4 ounces (1,928 Gm.) and later fell to 3 pounds 7 ounces (1,559 Gm.). At the age of 3 months the child did not move his limbs like a normal child. General weakness was noted in all extremities. During the following years the child was bedridden, requiring constant nursing attention. At the age of 6 years tendon-lengthening operations were instituted. They partially relieved the severe pain, but it was necessary to keep the patient under the influence of phenobarbital. During the last few years the vertebral column had become more curved, and the child had been subject to attacks of stiffness of all the extremities, especially on the left side. These usually consisted of sudden extensions of the extremities, accompanied by muscular pain. Passive flexion by other persons relieved the pain to some extent. The patient's general intelligence was good.

The family history was noncontributory.

Examination.—The patient was poorly nourished and had numerous deformities of the body, including pronounced lumbar kyphosis and lordosis, with the convexity to the right, and asymmetry of the thorax, the subcostal margin and the iliac crest on the left side approaching one another. The right thigh was abducted to an angle of 75 degrees; the right foot was dorsiflexed; the left thigh was rotated internally, with dorsiflexion of the foot to an angle of 80 degrees; the left arm was abducted to 90 degrees, with flexion at the elbow, wrist and fingers, and the right arm was held at the side and flexed at the elbow, wrist and fingers. He could not walk, sit erect or hold up his head. When he was on his back, there were episodes of tonic contractions, during which he went into opisthotonos; this occurred about every five minutes and lasted about a minute. These spasms appeared to be extremely painful. Muscular development was poor throughout. Speech was slurred. The reflexes were hypotonic.

Nothing abnormal could be found on neurologic examination.

Mental examination revealed a normally bright child.

Laboratory examinations showed nothing abnormal.

Operation.—The left anterolateral aspect of the cord, above and below the fourth cervical nerve root, was cauterized. Since then the patient has been able to rest comfortably in bed and sit up in a wheel chair.

Film Analysis.—Preoperative Series: The patient was lying on a stretcher (fig. 12 *D*), with the head turned to the left. There were extreme lordosis and kyphoscoliosis, and the upper part of the trunk was twisted to the left. The left arm was flexed and pronated at the elbow; the hand was flexed, and the fingers were tightly closed. The left leg was extended and lay on the stretcher; the right leg was extremely flexed at the hip and extended at the knee. The right foot was slightly dorsiflexed; the left foot was inverted and dorsiflexed. The right arm was kept over the head and appeared loose and without tension.

In this peculiar position the body rested only on the left shoulder and the left heel, and the patient had to be supported by the nurse in order to prevent him from falling down.

The position did not change for a while. Then the left foot went into inversion, and its dorsiflexion was increased. The extended left leg made slow swaying movements, but the extreme extension was not changed

After a while rotation of the head and lordosis were increased. Decrease and increase in tension of the muscles of the back appeared and disappeared at irregular intervals. Suddenly the right leg was flexed at the knee (fig. 12 *E*), but the flexion at the hip persisted; the right leg was kept for a long time in this position—flexed hip and flexed knee. Then another extension of the lower part of the leg began and was completed in four frames. Simultaneously, extreme inversion and dorsiflexion of the right foot and dorsiflexion of the big toe occurred, and the lordosis and twisting of the trunk increased. This position was maintained for the next few seconds; only slow swinging movements of the right leg were observed.

Close-up pictures showed no hyperkinesis of the face. There were some alternating movements of the left forearm, the right leg and the left leg and foot at irregular intervals. Inversion and dorsiflexion of the left foot were increased and decreased at irregular intervals.

A photograph of the back of the patient (fig. 12 *B*) shows the extreme lordosis and kyphoscoliosis. The child, lying on his stomach, held the left leg extended, while the right leg was flexed at the hip.

While the child was hanging supported around the chest in the arms of the nurse (fig. 12 *A*), the deformity of the spine and trunk was again evident, and both legs were in extreme extension. Suddenly the extended right leg was flexed at the hip. Later, slow, sustained athetotic movements of the right hand and fingers were observed on the same side (fig. 12 *C*). Hyperextension of the right leg was maintained for several minutes, i. e., for the whole run of the film.

Postoperative Series: The patient was lying on the stretcher in a much more comfortable position (fig. 12 *F*). Some lordosis was still present, but was far less extreme than before operation. There was no evidence of tension, change of position or involuntary movements except for athetotic movements of the left foot (fig. 12 *G*).

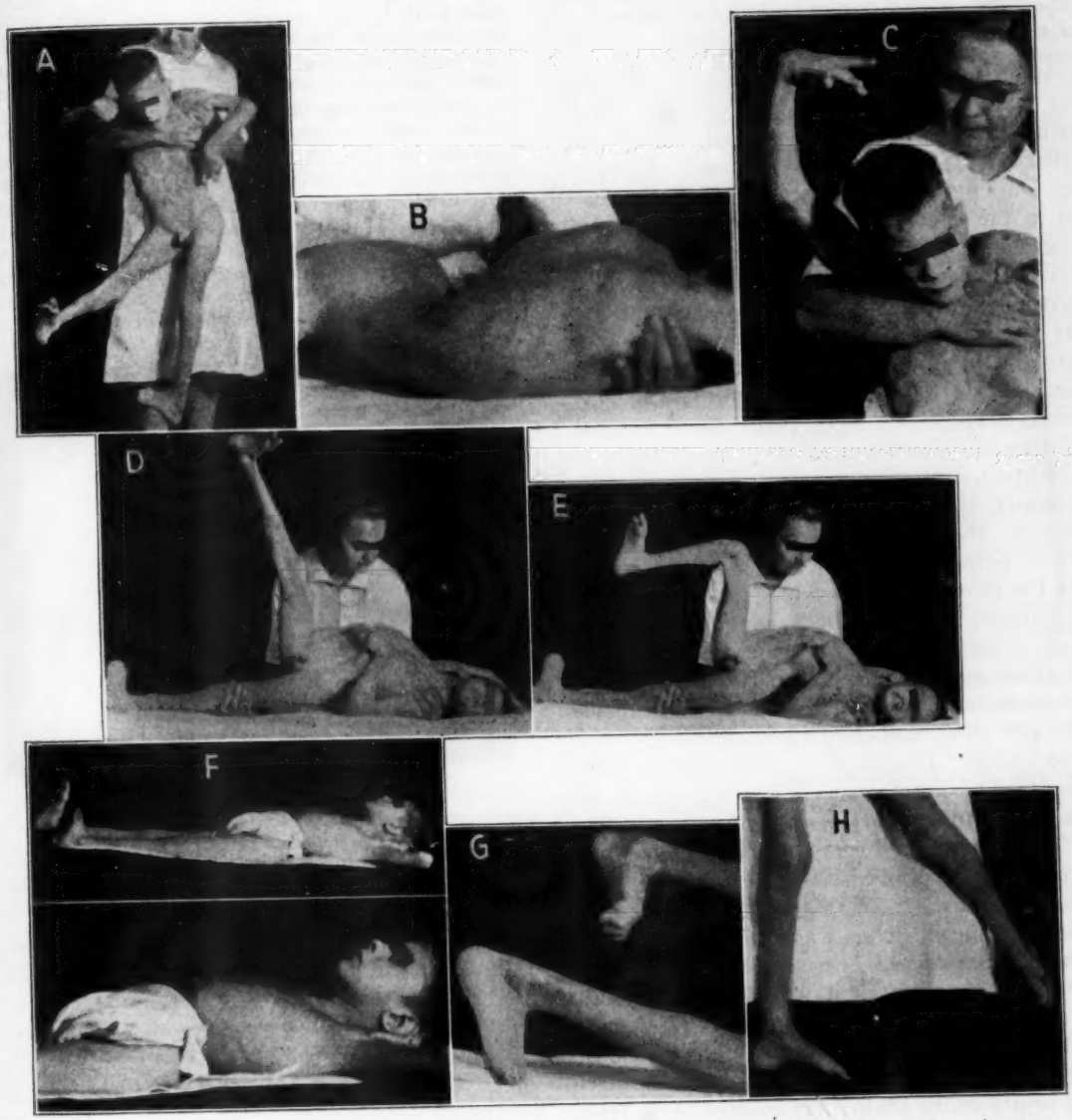

Fig. 12 (case 9).—*A*, *B*. *C*, *D* and *E*, preoperative pictures; *F*. *G* and *H*, postoperative pictures.

When the boy was hanging in the arms of the nurse (fig. 12 *H*), the left leg hung loose and showed no tension, and the right leg was again flexed at the hip and extended at the knee. Again there occurred slight swinging movements of the extended right leg, with inversion and dorsiflexion of the right foot, but there were no movements of the left lower extremity.

Photographs of the back show that lordosis and kyphoscoliosis were notably reduced but that the sustained tensions of the right lower extremity continued. (These were later largely relieved by a chordotomy on the right side.)

At birth, after a precipitate delivery, the child was underdeveloped, small and cyanotic. Motor disturbances, which were noticed shortly after birth, rapidly progressed to changes of posture. Tendon-lengthening operations had to be carried out at the age of 6 years. The disease rapidly progressed during the following three years, until a pitiable condition resulted.

At the time of observation, when the patient was 9 years old, peculiar postural distortions were the predominant symptom. Some of the positions were maintained continuously, even during sleep. They were partly due to changes in bones and shortening of tendons and muscles. In addition, dystonic movements appeared, caused transitory changes in the position of different parts of the body and were maintained for various periods. The disorder was widespread; only the face was completely spared. The hands and fingers showed slight involuntary movements, which were best characterized as athetotic. The trunk and the proximal parts of the extremities were most affected by the postural distortions and slow, sustained movements.

No other neurologic abnormalities were present. The involuntary motor activity, in the form of dystonic movements and postures, was the sole symptom. From the clinical viewpoint the condition in this case was, again, an elective systemic disease.

Notable in this case was the early onset of the motor disorders. They were noticed shortly after birth, as soon as it was possible to form an opinion about motor abilities. The newborn child was underweight and underdeveloped in total function, but no gross signs of a localized birth injury of the brain were evident. Outstanding were the rapid progression of the disturbances and the wide distribution of the tension and the postural disorders.

In the case of such an advanced condition, in which permanent contractures have been formed, only partial relief can be expected from a surgical procedure. The decrease of tension on the side of operation (left) was clearly recognizable. The curvature of the spine was somewhat reduced, and the left leg showed less dystonic tensions than the right. The subjective condition of the patient was much improved. The sustained tension had caused strange feelings, which were described as pain. After operation the intensity of these feelings was remarkably decreased.

Case 10.—*History.*—M. B., a youth aged 18, who was referred by Dr. Leo Davidoff, was admitted with a history of motor difficulties since early childhood. He was born after a normal, full term pregnancy, which was terminated by instrumental delivery. Immediately after birth he had several convulsions, which recurred for several days, but had never appeared since. Early development was slow, and he did not begin to walk until he was 2½ years of age. Then he had difficulty in walking because his gait was stiff. This stiffness became more pronounced when he was excited or nervous, but he was able to play ball and get around fairly well. In 1931 section of the obturator muscle was done on both sides in order to correct the difficulty. This operation made it possible for him to walk on the entire foot, instead of on the toes only. Shortly before the operation the patient noticed that he was having movements of the extremities, and since the operation these movements had become constantly worse.

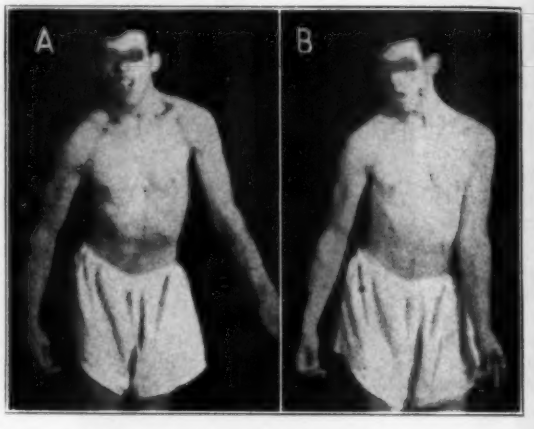

Fig. 13 (case 10).—Dystonic posture and movements.

They involved all parts of the body, including the face, tongue and neck. He stuttered when talking too fast, and the words came forth in an explosive manner. When he was relaxed the patient could write, play ball or read the paper aloud to members of his family. The patient felt that when he was relaxed the movements completely disappeared.

Examination.—The musculature was well developed, but there were thoracolumbar scoliosis and a scissors gait. Strength was generally good. Speech was explosive, with pronounced stammering and stuttering and an element of dysarthria. The reflexes could not be tested because of the tense state and involuntary movements. The right pupil was greater than the left, and the reactions were normal. The mental status was normal.

Laboratory examinations revealed nothing abnormal.

Operation.—The anterior half of the left lateral column of the cord was cauterized at the level of the second cervical segment, through a laminectomy opening, on Oct. 21, 1941. The patient was discharged, with improvement in gait and remarkable reduction in involuntary movements of the extremities of the left side.

Film Analysis.—When the patient was standing (fig. 13 *A* and *B*), the trunk was slightly bent and turned to

the left. The head was turned to the right. There was severe hyperkinesis of the trunk, shoulders and both upper extremities, consisting of the following components:

(1) slow, irregular movements at irregular intervals with continuously changing pattern, the trunk and the proximal parts of the extremities being involved more than the hands and fingers, and

(2) quicker, alternating movements at irregular intervals with uniform pattern.

Slow motion pictures revealed the irregularities of sequence and pattern and showed clearly that the long-sustained movements of the trunk and the proximal parts of the extremities were more frequent than the athetoid movements of the hands and fingers.

Analysis elicited, for example, the following pattern: twisting of the trunk, turning of the head to the right, abduction of the left arm, dorsiflexion of the left hand and extension of the left index finger. Then the extended left arm was brought forward in a circle and held for a while in an elevated, extended position. Then the left arm as a whole was swung backward, and, at the same time, the left shoulder was elevated and the right arm extroverted and adducted.

The alternating movements were quick and unsustained and followed one another at irregular intervals. Close-up and slow motion pictures of the head and shoulders showed alternating raising and drooping of the shoulder girdle with interposed turning movements of the head to the left.

A close-up picture of the arms and hands showed that the throwing movements of the whole arm were more frequent than the slow, sustained movements of the hand and fingers.

When the patient was walking the disorder of posture was increased. The trunk was turned and bent farther to the left. Gait was much interfered with by the involuntary movements and by sudden, long-sustained tensions of the adductor muscles and sustained rotation of the right leg.

Four Weeks After Chordotomy.—The quick alternating movements of the shoulder girdle and the arms were not much influenced, but the slow, sustained movements and tensions of the trunk and the upper extremities were visibly reduced on both sides.

There was no paresis of the upper or lower extremities on either side. In walking the patient still showed the swinging movements of both arms. The right leg showed some adduction and inward rotation, whereas the left lower extremity was much looser than before.

In this case the boy had several convulsions immediately after delivery; these seizures had never recurred. Muscular tensions of changing intensity, which were noticed shortly after birth, produced impairment of motor abilities. Long-sustained abnormal positions of the lower extremities made walking difficult. A tenotomy was carried out because of the tension. At the age of 8 years alternating movements appeared, in addition to the dystonic symptoms.

The condition progressed slowly but continuously. At the time of observation, when the patient was 18 years of age, dystonic movements of the muscles of the neck, shoulder girdles and back were pronounced. Longer-sustained contractions appeared at irregular intervals in the trunk and caused postural disorders, whereas sustained tensions of the adductor and extensor groups of the lower extremities severely interfered with the act of walking. Sometimes, when the tension came on in both adductor groups simultaneously, a gait similar to the so-called scissors gait, characteristic of bilateral pyramidal lesions, resulted. But bilateral dystonic tensions can be differentiated from stiffness caused by spasticity. Dystonic tensions come on at irregular intervals; they are maintained for various periods, and periods of relaxation—sometimes of long duration—were seen between them. Analysis of the film showed alternating movements (myorhythmia), in addition to the dystonic movements. No other abnormalities were revealed by the neurologic examination. The symptoms, again, were confined to the appearance of involuntary motor activity.

From the clinical data available, it must be assumed that a disorder of the brain was present at birth. Significant are the elective symptoms, confined to involuntary motor activity, and the mild course, with relatively slight progression up to the age of 18 years.

The anterolateral chordotomy on the left side brought about remarkable reduction of tension on the side of operation, whereas the alternating movements persisted unchanged.

CASE 11.—*History.*—G. S., a white youth aged 20, was admitted to the hospital in February 1940, complaining of generalized movements of the arms and legs.

The family history was essentially noncontributory. Birth was normal, at the end of an eight months' pregnancy. At the age of 1 month the patient was unable to suck his right thumb as he had done before and his right arm tended to straighten out and move backward. These symptoms increased in severity, and wormlike movements, first of the right arm, later of the left arm and then of both legs, gradually appeared. These writhing movements had increased in severity over a period of twenty years, but they had become definitely worse since the age of 5 years, when the patient had the first of a series of convulsions. The seizures recurred at the ages of 9 and 14, each period being about six months. During the convulsive seizures the patient's arms and legs went into extreme extension, and the neck and back were extended forcibly in the form of opisthotonos.

Ever since the onset of the involuntary movements the right side had been more affected than the left. The patient had been unable to help himself in any way since the age of 5 years and had spent the greater part of his time in a specially constructed chair, with a strap across his abdomen, his right arm doubled up behind his back and his head and neck turned to the right.

Examination.—There were pronounced cervical, thoracic and lumbar scoliosis, with a definite deformity of the thorax, and generalized muscular atrophy, greater on the right side than on the left. The patient was unable to grip well with either hand, although the grip of the left hand was slightly stronger than that of the right. The reflexes appeared equal and normal in the arms and slightly increased in the lower extremities.

There were no pathologic reflexes. Examination of the cranial nerves revealed no abnormalities.

Laboratory studies revealed nothing significant.

Operation.—After a cervical laminectomy, the ventral roots of the second and third cervical nerves were crushed on both sides; the spinal accessory roots were cut bilaterally, and a ventral chordotomy was performed on the right side.

Film Analysis.—The patient was sitting, or rather lying, on his chair, with high arm supports and supports for the head and feet (fig. 14 *A*).

During the observation the head was turned to the right, and the trunk, particularly the upper part, was twisted to the right. At irregular intervals sustained tensions appeared in the upper and lower extremities. They brought on changes in position of the whole arm, forearm, hand, thigh, leg or foot of irregularly changing patterns. In addition, there were turning movements of the head. It was easy to see when the tensions relaxed and the affected part became loose again. There were slow movements of the hands and fingers but no involuntary movements of the face.

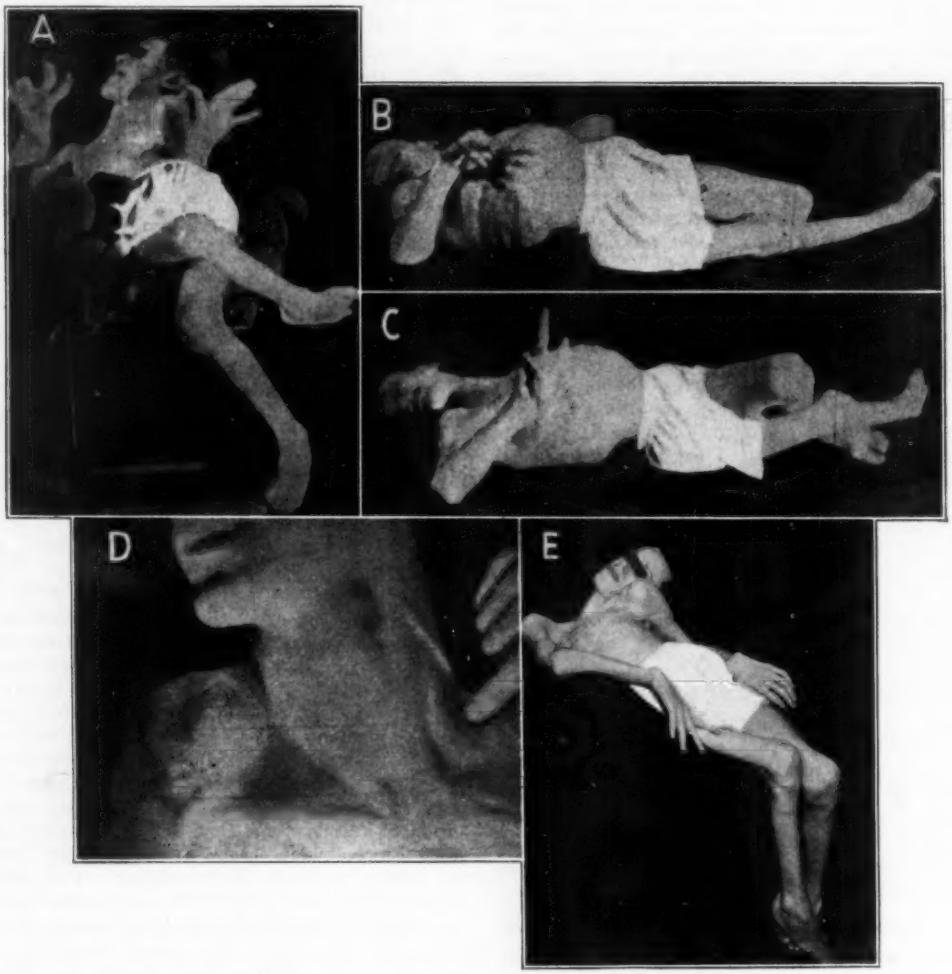

Fig. 14 (case 11).—*A*, *B*, *C* and *D*, preoperative pictures; *E*, postoperative picture.

The trunk was extremely distorted. The upper part was bent to the left at an acute angle. The lower part and the pelvic portion were twisted around to the left. The head was extended. The upper portion of the right arm rested on the arm support, and the forearm was extremely flexed at the elbow and extremely pronated. Each of the fingers was in a different position, being either flexed or hyperextended. The left arm was also fully flexed at the elbow, and the upper part of the arm was pressed against the chest. The hand and fingers on the left side were held in a fashion similar to that on the right. The lower extremities were flexed at the hips and knees, and both were extremely adducted, so that the two thighs crossed. The left foot was plantar flexed and supinated.

When the patient was lying on the floor (fig. 14 *B* and *C*), the extreme distortion of the trunk was again visible; in addition, the tremendous lordosis could be seen. Otherwise, the posture was almost the same as that already described.

Suddenly a burst of involuntary movements appeared, with long-sustained turning of the head to the right and flexion of the forearms at the elbow. Then the right arm was adducted at the shoulder, and the left arm was lifted in front, with flexed elbow, and kept in this position for some time. The forearm was then extended and later flexed. Then followed a transient increase in the distorted position of the trunk.

A close-up series of the head and neck (fig. 14 *D*) showed long-sustained contraction of the left sterno-

cleidomastoid muscle and slow contractions of the deeper cervical and pectoral muscles, particularly on the left side. The head was held turned far to the right.

There was strong resistance to passive movements of the upper and lower extremities only as long as the tensions were present. Then, suddenly, the resistance disappeared completely and passive movements could be carried out easily. Such periods of relaxation were observed at the elbows, wrists and ankle joints. They were rarely noticeable at the hips.

Four Weeks After Operation: The patient was sitting on his chair in a much more relaxed position than before operation (fig. 14 *E*). The head rested on the left shoulder; there was still extreme lordosis, and the trunk was twisted to the right. The legs were not crossed. No tension or particular position was noticeable in either the upper or the lower extremities. Suddenly, the right arm slipped down from the arm support and hung waving loosely, like a pendulum. There were many more involuntary movements of the hands and the fingers of the right hand than before operation.

A close-up of the head and neck showed that the muscles of the neck were completely relaxed. Passive movements of the right arm showed no tensions. Movements in the shoulder, elbow and wrist were loose.

This boy was born after a pregnancy of eight months; delivery was normal, and he did not show any abnormalities in the first weeks of life. But at the age of 1 month abnormal motor activity of the right arm was noticed. The hyperkinesis gradually increased in severity and spread over the whole body. There certainly was a continuous progression of the motor symptoms, but a remarkable aggravation of the disorder set in at the age of 5 years, after a series of convulsions. The seizures recurred twice at the age of 9 and 14 years, and have not appeared since.

During observation, when the patient was 20 years old, dystonic movements of the neck, shoulders, back and all four extremities came on in continuously changing pattern and with varying intensity. Transient postural distortions were maintained for various periods, in addition to permanent postural changes, especially of the trunk and the proximal parts of the extremities. A pitiable condition resulted, in which almost all voluntary motor activity was frustrated.

No other significant abnormalities were revealed by the neurologic examination. The general muscular atrophy was certainly due to disuse. Its distribution and the accompanying signs and symptoms, such as the state of the reflexes, did not suggest a neurogenic disorder.

There may be doubt as to whether the motor activity in the first weeks of life was really normal. In any case, it must be assumed that a disorder of the brain was present at birth. The elective systemic motor symptoms produced by this process progressed rapidly. Remarkable in this case, with the early onset of dystonic symptoms, was the occurrence of a series of convulsions. From the description, they consisted of epileptic seizures of predominantly tonic character, and not of a transient increase in dystonic tensions. Such epileptic attacks are rare in cases of systemic disease with involuntary movements. Epileptic attacks are infrequently associated with either degenerative diseases or inflammatory processes, such as chronic epidemic encephalitis, but they occur occasionally (case 46 of Herz). They may have been brought on in this case by a sudden, particularly severe progression of the pathologic process in the brain.

The operative procedure aimed at relief of the torticollis was successful. The anterolateral chordotomy brought considerable reduction of tension on the side of operation. The right arm was loose and pendulous, but, simultaneous with the reduction of long-sustained contractions, many more involuntary movements were seen in the distal parts (hands and fingers) after operation. The effect of the operation has been considerably enhanced by subsequent muscle training.

CASE 12.—*History.*—G. K., a white man aged 43, referred by Dr. Samuel Brock, was admitted to the hospital in April 1940. His birth is said to have been difficult, delivery requiring forceps, but his early development was alleged to be normal. At the age of 2 years he had an acute febrile illness in which he was comatose for forty-eight hours; no further information about this illness was available. It was noticed that at the age of 4 years he kept his left index finger extended and his thumb flexed, and at about the same time he began to display mild tremor of the left hand. About a year later he began to carry his left arm flexed at the elbow and adducted over the chest. This complaint persisted. At the age of 6 his gait became somewhat jerky, with dragging of the right foot. Since the age of 14 his right lower extremity had frequently become flexed and adducted at the hip and flexed at the knee. The foot assumed an equinovarus position, with the toes resting on the floor. Since the age of 12 or 14 he had been troubled by jerking movements of the right shoulder, which interfered with the use of his right hand. At the age of 17 he had a sudden onset of wryneck and jerking of the head, the face looking to the right. In 1931, after a disappointment, the patient had an episode of unconsciousness, and since then the disturbances in his right extremities had been more noticeable. Alcohol and barbiturates produced some improvement in his symptoms.

Examination.—The right side of the face was larger than the left. There was scoliosis of the spine, with the concavity to the left. The gait was stiff, with the feet somewhat supinated and inverted. There was moderate spasticity of the extremities on the left side, but muscle power was good bilaterally, strength being slightly better on the right side than on the left. The tendon reflexes were fairly brisk, with slightly greater prominence in the left lower extremity, and a spontaneous Babinski sign was present bilaterally. The cranial nerves were normal.

The level of intelligence was apparently high.

Laboratory studies revealed nothing abnormal.

Operation.—A high cervical laminectomy was done, and the upper three anterior cervical roots were sectioned bilaterally. The spinal accessory nerves were

crushed, and a ventral chordotomy was performed with cautery on the right side.

At the time the patient was discharged, the neurologic status resembled that on admission except that the jerking movements of the head had disappeared and the right hand was more relaxed.

Film Analysis.—When the patient was standing (fig. 15 *A*), the head was turned to the right and bent to the left. The left shoulder stood higher than the right. The left arm was adducted and slightly flexed at the elbow. The left hand was closed. There was kyphoscoliosis, with arching of the spine to the right. The right arm hung in a natural position. The legs were held apart.

A close-up series of the head showed the typical position of torticollis (fig. 15 *B*). There were some irregular contractions of the sternocleidomastoid muscle and the deep muscles of the neck, particularly on the right side.

In walking the patient exhibited more pronounced change of posture; the head was more twisted to the right, and the scoliosis was intermittently increased, reverting to the former degree at irregular intervals. Sometimes the flexion of the left elbow was increased, and the end position was maintained for a few seconds before the tension relaxed.

A close-up photograph of the back (fig. 15 *C*) showed extreme lordosis, especially of the thoracic portion of the spine, kyphoscoliosis and torticollis. There were slow, irregular, sustained contractions of the muscles of the back at irregular intervals, in addition to continuous contraction of the right erector muscle of the trunk. These contractions resulted in irregular movements of the whole arm, but sometimes only the contraction of the muscles of the shoulder blade was visible, without motion of the arm.

Close-up and slow motion pictures of the extended left forearm showed irregular, alternating movements of the hand at the wrist joint and of the individual fingers and the thumb. The intervals between the alternating units varied, and the pattern changed continuously. When one concentrated on the movements of the index finger exclusively, it was possible to make out flexion and extension, adduction and abduction, following each other in rather irregular sequence. The thumb made alternating movements, changing from one direction to another. Sometimes the end position of a movement of extension or adduction was maintained for a time. Various positions of the individual fingers were also maintained at times, with arrest of the alternating movements.

During certain acts, such as lighting a cigaret or drinking a cup of water, the hyperkinesis was greatly increased. Slow, sustained movements of the head, shoulders and arms occurred, in addition to alternating movements of the hands, forearms and right leg. The act was seriously interfered with by these involuntary movements and tensions. For instance, a paper cup was compressed by sustained flexion of the fingers as it was being brought to the mouth, and the water was spilled. In slow motion pictures one could clearly see the different involuntary movements which were brought on by voluntary action—in the shoulders and upper part of the arm more than in the forearm, hand and fingers. It was striking that the spontaneous hyperkinesis of the left side was mild. But voluntary acts caused involun-

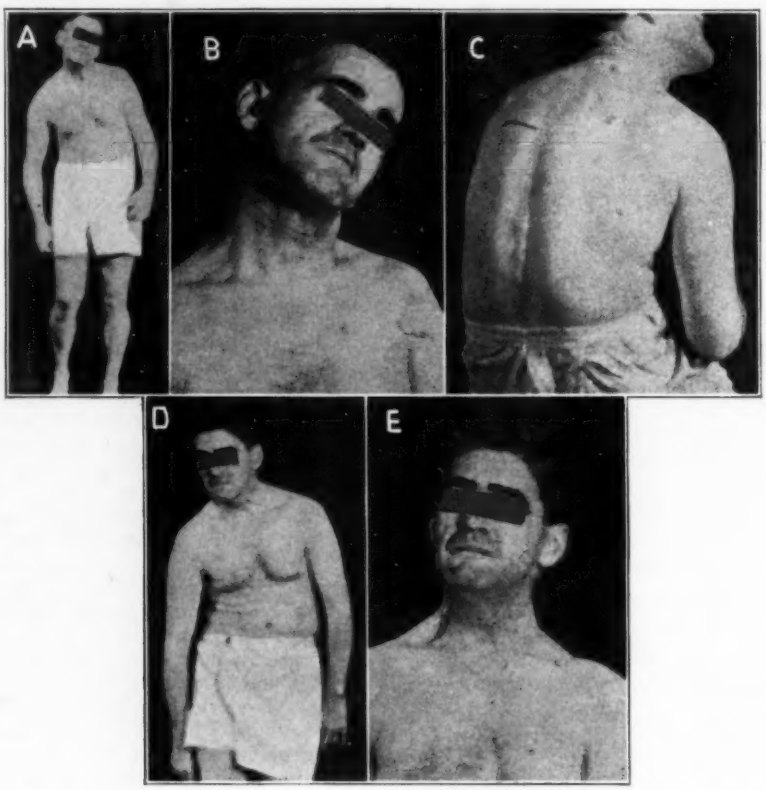

Fig. 15 (case 12).—*A*, *B* and *C*, preoperative pictures; *D* and *E*, postoperative pictures.

tary movements which were almost as severe on the left side as on the right, where the spontaneous hyperkinesis was more pronounced.

After operation the position of the head is much improved. It is now held almost straight. But the position of the trunk and extremities is unchanged (fig. 15 *D* and *E*). The postural disorder and involuntary activity, both spontaneous movements and those induced by voluntary action, are not decreased. The range of voluntary movements of the head is somewhat reduced.

The history of the development of the disease in this patient is complicated. Delivery was difficult, but signs of injury of the brain at birth were not noted and development was normal in the first two years of life. At the age of 2 years the child had an acute illness, the nature of which could not be determined. The presence of a comatose condition creates the presumption that the nervous system was somewhat affected. When he was 4 years old, involuntary motor activity started in the left arm and left hand, without any recognizable cause. The motor disorder was steadily progressive during the next twenty years. An increasing number of parts were affected: the extremities, the trunk and the shoulders. At the age of 17 the neck became involved, with the appearance of extremely disturbing torticollis, and at the age of 31 further progression was reported, after an episode of unconsciousness.

Analysis of the motor symptoms revealed slow dystonic movements, which were maintained for different lengths of time and came on at irregular intervals. In addition, changes of posture were present, and abnormal positions brought on by dystonic tensions were maintained for longer periods. Alternating movements, with the characteristics of myorhythmia, occurred more often in the left arm and hand than in the right. Voluntary acts were severely interfered with by the involuntary hyperkinesis. On the right side, where the spontaneous hyperkinesis was much less pronounced than that on the left, the impairment of voluntary movements was as great as that on the left.

Neurologic examination revealed spasticity of the left extremities and greater prominence of the tendon reflexes in the left lower extremity. The Babinski sign was present bilaterally.

In this case the symptoms were not of an elective systemic character. Although dystonic symptoms were prevalent, the signs suggesting lesions of the pyramidal system cannot be neglected. The occurrence of an infectious disease, with apparent involvement of the brain, two years before the onset of the hyperkinesis must also be considered. Although there was a free interval between these two incidents (the disease of the nervous system and the onset of the involuntary movements), the disease, starting at the age of 4 years, may have been caused by a lesion produced by the infection at the age of 2 years. On the other hand, the steady, slow progression of the disease, with dystonic symptoms, was similar to the course in cases in which no etiologic factor is recognizable.

It is probably wiser not to attempt classification of such complicated cases. They should be taken out of the dystonia group and considered separately until pathologic examination furnishes the explanation.

The part of the surgical procedure aimed at relief of the torticollis was successful. After the operation the head could be held straight, and no twisting occurred. The result of the anterolateral chordotomy was not convincing, but the patient reported that he had considerably more freedom in the use of his hand and trunk.

CASE 13.—*History.*—C. W., a man aged 23, was admitted to the hospital with a history of spasticity and involuntary movements since birth. Pregnancy, labor and delivery were apparently normal in every respect. The patient was a first-born child; his weight at birth was 5 pounds 6 ounces (2,388 Gm.). No abnormality was noticed until the age of 6 months, when he seemed to be unable to sit up. He continued to be clumsy and to balance poorly and did not walk until he was 4 years old.

Because of the stiffness and the uncontrolled movements of the left extremities, he was severely incapacitated, although he was able to go through public school and to complete two years of high school. At the age of 8 years he had an operation for correction of the deformity of the left foot, and at the age of 18, a second operation and transplantation of the tendon. Subsequent to the last operation the involuntary movements of the left arm were accentuated. In March 1941 administration of scopolamine was started, as a result of which he was free from symptoms for several weeks; subsequently, however, the medication has had a gradually decreasing effect.

The family history was noncontributory.

Examination.—The patient was unable to walk without assistance. The left arm showed pronounced spasticity and a tendency to pull around behind the back. There were rigid spasticity of the muscles of the forearm and flexion of the fingers. The left leg was in general smaller, and perhaps shorter, than the right leg. Muscular strength was good on the right side but could not be tested for in the left arm. The left leg appeared to be generally weak. Tests for coordination and equilibration could not be performed. The deep reflexes were present and normal on the right side but were not satisfactorily obtained on the left because of spasticity.

The sensory status was normal. The pupils were equal and reacted somewhat poorly to light. The palpebral fissure was slightly greater on the left side than on the right, and there were many involuntary movements of the muscles of the left side of the face. The rest of the cranial nerves were normal.

Laboratory studies revealed nothing abnormal.

Psychometric examination revealed a high average general intelligence.

Operation.—In November 1941 temporoparietal craniotomy was done on the right side, and procaine hydrochloride was injected into various portions of the right

cortex. No change in the movements was produced until the drug was injected into the summit of the precentral gyrus, near the midline, when palsy of the left arm appeared and the involuntary movements ceased. About 3 Gm. of tissue was excised. After an uneventful postoperative course, the patient manifested slight voluntary motor power in the left upper extremity, with decrease in the involuntary movements. The voluntary power was not of useful character or amount at the time of discharge.

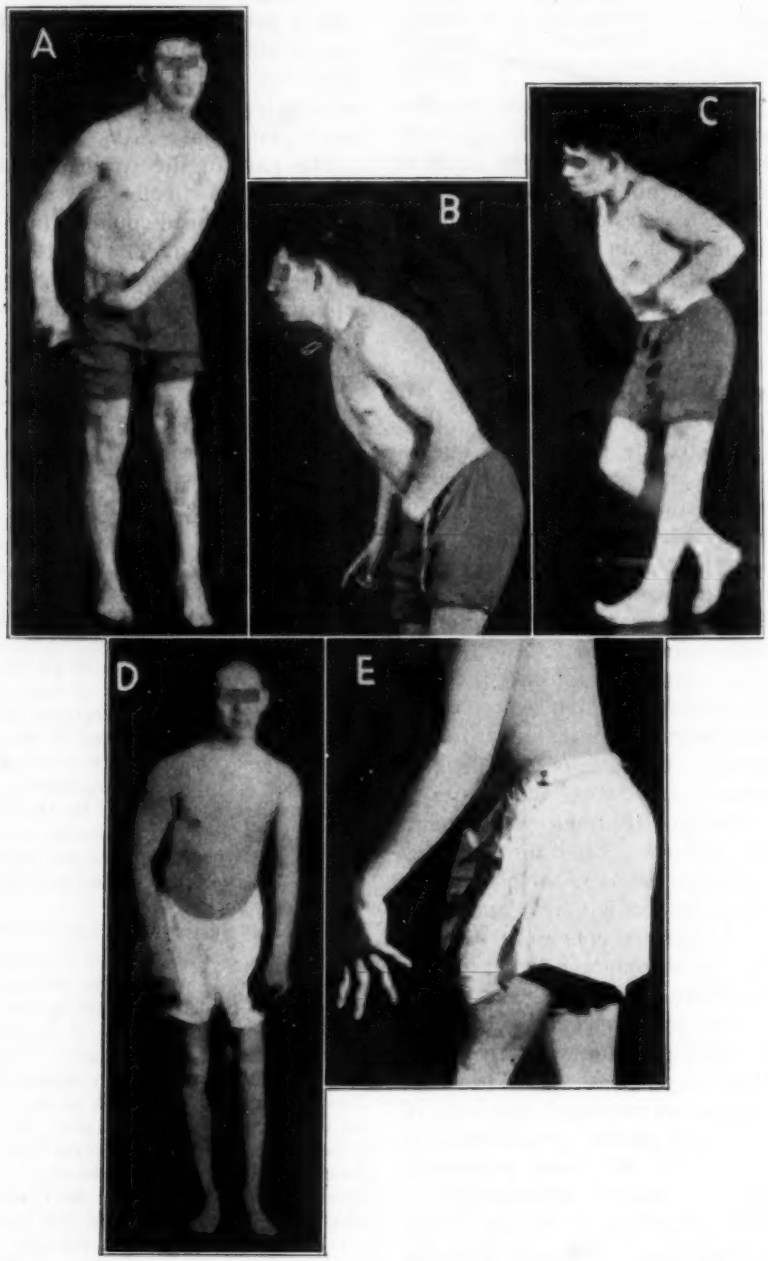

Fig. 16 (case 13).—*A*, usual posture; *B*, and *C*, increase in involuntary movements of left arm when the patient is turning around (*B*) and walking (*C*); *D* and *E*, appearance of hands eighteen days after operation. Note change of posture and increase of involuntary movements of left hand and fingers.

Film Analysis.—The usual posture of the patient was as follows (fig. 16*A*): The upper part of the body was slightly turned to the left and flexed; the head was hyperextended, and the body rested on the right leg. The left leg touched the ground only with the tips of the toes. The left arm was extremely adducted, there being slight flexion at the elbow. The hand and fingers were fully flexed. The right arm was freely movable and showed many reactive movements, but no involuntary hyperkinesis or tensions. At irregular intervals involuntary movements appeared in the left upper and lower extremities and in the trunk. Flexion and torsion of the trunk gradually became more pronounced, and flexion of the wrist and elbow increased until the elbow

was at an angle of about 15 degrees to the upper part of the arm. The upper part of the arm was rotated backward, and as the flexion of the elbow relaxed, the arm was brought and kept as far back as possible. At the same time that the left leg was fully extended, the left foot was held in extreme plantar flexion, combined with inversion.

Every phase of the movements was sustained for a long time. The sudden change from the sustained posture is seen in figure 3 of the first article. The plantar flexion and inversion of the left foot were maintained for at least a few minutes. Suddenly, between *3* and *4*, the position changed, i. e., in one-sixteenth second.

Slow motion pictures revealed that there was no regular synergism between the various movements, that is, flexion of the elbow, adduction of the arm and twisting of the upper part of the body, which were always long sustained. There were fairly long intervals, without any movements in which the usual posture just described was maintained. During the entire series no movements of the closed fingers of the right hand were observed. The gait was impaired because the left leg was smaller and shorter than the right. Furthermore, balance was disturbed by extensive torsion and flexion of the trunk. Soon after the patient started to walk, involuntary movements set in and were sustained for a long time. Balancing movements of the right arm were abundant, but not sufficient. He fell unless he was supported. The involuntary movements of the left arm were increased when he turned around (fig. 16 *B*) and when he was walking (fig. 16 *C*).

The pictures taken eighteen days after operation showed a habitual posture quite different from that before operation (fig. 16 *D*). The trunk was only slightly bent to the left and was not twisted. The left hand was open, and the fingers were extended. At irregular intervals irregular, slow, sustained finger movements occurred (fig. 16 *E*), consisting of hyperextension and flexion of the fingers and thumb in completely irregular pattern and sequence, sometimes combined with a passing flexion of the hand. In a fairly long series, no involuntary movements of the entire left arm could be seen, and only slight twisting and bending of the trunk appeared. As the patient began to turn around, involuntary movements of the whole arm, with flexion at the elbow and adduction at the shoulder, occurred, but these movements were not so pronounced as before operation. During this voluntary action (turning around) the left hand was kept open, and there were extensive involuntary movements of the fingers.

There was pronounced paresis at the shoulder and elbow. Movements of the hand and fingers were carried out fairly well. During voluntary movements with the left arm and hand some twisting and bending of the trunk occurred.

The gait was much improved. There was no sustained tension of the left leg. Twisting and bending of the trunk were present, but were not so severe as before.

Birth was apparently normal, and no abnormalities were noticed in the first months of life. At the normal period for the appearance of coordinated motor activity, first clumsiness and then stiffness and involuntary movements of the left side of the body became apparent and persisted. General development of motor abilities was slow, and the growth of the left leg lagged behind that of the right.

Neurologic examination at the age of 23 revealed disturbances only on the left side. Pronounced stiffness of the upper and lower extremities on the left side was due to spasticity, aggravated by tensions which varied in intensity and were not constantly present. This stiffening factor produced peculiar postures of the extremities and the trunk when the muscles of the back participated. These postures showed variations in pattern and intensity. Sometimes a posture seemed to be due to a permanent contracture, resembling that associated with hemiplegia. But analysis of the film demonstrated fine differences in the positions of parts of the body. The plantar flexion and inversion of the left foot seemed to be permanent, but during the observation of a long series of pictures it suddenly disappeared from one frame to the next. The speed of this change of position can be explained only by the sudden disappearance of the additional stiffening factor.

The result of the cortical operation (extirpation of the right precentral gyrus) was remarkable. The stiffness and the tendency to transient tensions were considerably reduced. But whereas before operation the left hand was tightly closed and could be opened only after relaxation, involuntary, athetotic movements of the fingers were present after operation. They appeared predominantly as associated movements when the patient carried out voluntary acts.

The spastic hemiparesis, with underdevelopment of the left lower extremity, was presumably due to a discrete lesion of the brain stem which affected the pyramidal tract and structures lesions of which produce dystonic tensions. In spite of the report that abnormalities were not noticed during the first months of life, the disorder may have been present from birth, as motor disturbances sometimes do not come to the attention of parents before the development of motor abilities is expected. For this reason it cannot be determined whether the lesion of the brain was due to injury at birth or to an inflammatory process occurring before or shortly after delivery. In any case, the disorder started in early childhood and became more apparent only in later life, but did not really progress.

The course and the symptoms of the disease suggest the presence of a discrete lesion acquired in early childhood, and not an elective systemic disease with a tendency to progression. This case should not be included with the cases of dystonia.

CASE 14.—*History.*—E. S., a white man aged 25, entered the hospital for consideration of operative treatment.

His father was said to have been mentally defective; a paternal aunt was an imbecile and a dwarf, and a paternal uncle had a high temper. The patient's brother was "nervous."

After the patient's delivery he did not breathe spontaneously for about an hour. In the first few months of life he appeared to sleep during the daytime and cried all night. He began to walk at the age of 3 or 4 years. At the age of 7 or 8 the patient was called "Limpy," a nickname indicating that he walked with a limp. However, he was able to play games and maintain the pace set by the other boys. At the age of 14 he noticed his defect more, and his writing became poor because he pressed too hard on the paper. In the six years preceding admission to the hospital the difficulty became more severe. When he was 19, his left hand began to draw up in a rotated position, and he found it difficult to relax his muscles. He was always able to relax after he had had a number of drinks. From the age of 14 to that of 17 he was chronically drunk.

Examination.—The patient was well nourished and well developed but pale. Enlargement of the lymph nodes was noted in the left supraclavicular and the right anterior cervical group. The blood pressure was 148 systolic and 90 diastolic.

Neurologic examination revealed that the patient was left handed. The position of the extremities and the involuntary movements will be described in analysis of the film. In walking he exhibited a steppage gait, especially noticeable in the right foot, with scraping of the toes. His voice showed jerky alterations in volume. The reflexes were difficult to elicit in the left arm and could not be obtained in either leg. No pathologic reflexes were present. The abdominal reflexes were more active on the right side than on the left. At times the right pupil appeared smaller than the left, and the reaction to convergence was slight on both sides. When the patient was speaking, the left side of the face showed less innervation than the right.

The patient had a fairly well ordered mind but was emotionally unstable.

Laboratory investigations revealed nothing abnormal. Roentgenograms of the skull and the electroencephalogram showed nothing significant.

The patient was advised to submit to an operative procedure but decided against it.

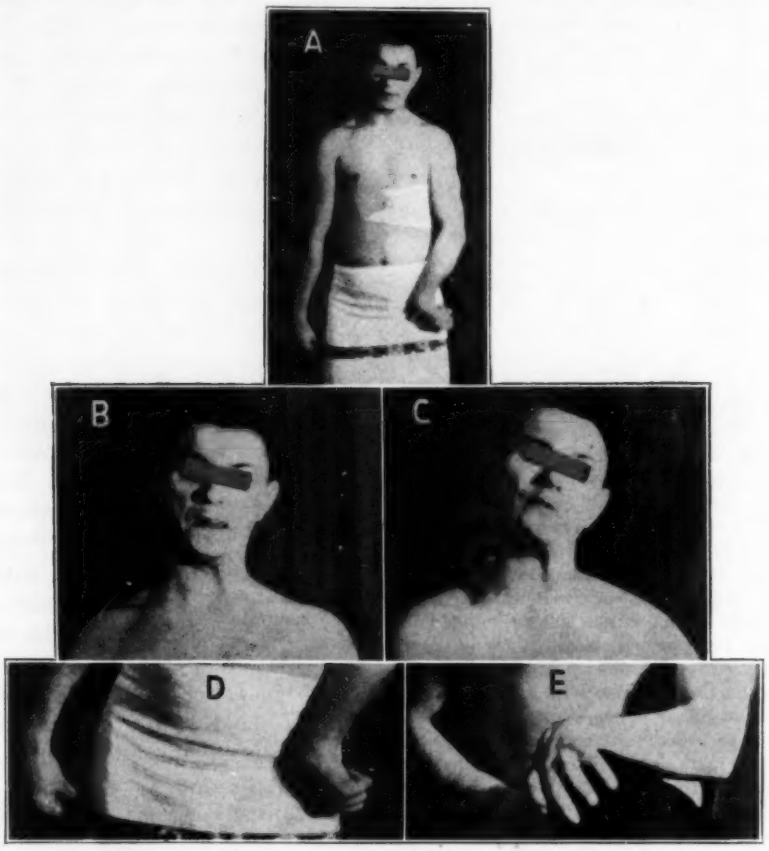

Fig. 17 (case 14).—*A*, spontaneous posture; *B* and *C*, involuntary movements of left side of face and sustained contraction of platysma muscle; *D* and *E*, voluntary opening of usually closed hand.

Film Analysis.—The patient stood (fig. 17 *A*) with the whole body slightly inclined to the left. The right arm hung in a natural position. The left arm was adducted at the shoulder joint. The forearm was slightly flexed and pronated. The hand was extremely flexed at the wrist (fig. 17 *D*). The fingers were also flexed, but the degree of flexion changed at irregular intervals and differed with each finger.

A close-up picture of the upper part of the body showed (*a*) slow, irregular movements of the muscles of the face, more noticeable on the left side than on the right, and (*b*) slow contractions of the superficial and deep muscles of the neck at irregular intervals, with some long-sustained contractions of the left platysma muscle (fig. 17 *B* and *C*). When the patient counted,

the hyperkinesis of the muscles of the face and neck was much increased.

A close-up view of the left forearm and hand as they were supported by the examiner showed that the patient was able to open his hand and to reduce the flexion of the wrist voluntarily (fig. 17 *E*). Alternate opening and closing of the hand was sometimes interrupted by extreme flexion of the wrist and of the fingers, with adduction of the thumb. After a while the tension relaxed, and the alternating movements were resumed.

If the patient pressed the hand of the examiner with his right hand, extreme tensions of the left hand and the fingers appeared, as synergistic movements. The patient could not overcome the flexion of the hand and fingers, and voluntary movements of the left hand were impossible while he was pressing with the right hand.

In walking he showed some circumduction of the left leg, with dropping of the foot. Associated movements of the left arm, which was held in the aforedescribed position, were remarkably less than those of the right arm.

The patient came of a family with several defective members. After his delivery he showed severe general disturbances, which suggested an injury of the brain at birth. Left hemiparesis had been present since early childhood, and the development of motor functions was retarded. Involuntary movements and tensions appeared much later. At the age of 14 years voluntary action, particularly that of writing, was interfered with, but not before the age of 19 did dystonic movements and sustained tensions become conspicuous.

Neurologic examination at the age of 25 revealed left spastic hemiparesis with slow, involuntary movements of the corresponding side of the face, long-sustained dystonic movements of the platysma muscle and the superficial and deep muscles of the neck and extreme tensions of the upper and lower extremities, all on the left side. The almost constant flexion of the left hand and fingers was not due to a spastic condition. When relaxation occurred spontaneously or was brought about voluntarily, voluntary movements could be carried out, although they were suddenly arrested by involuntary tensions and abolished for some time. These dystonic tensions appeared sometimes as associated movements. When, for instance, strong voluntary movements were carried out with the right hand, tensions appeared in the left hand. The left hand could not be relaxed voluntarily before the voluntary movement of the right hand ceased.

In this case the dystonic phenomena were associated with spastic hemiparesis. There is no question of the presence of an elective systemic disease. A discrete lesion of the brain, probably caused by birth injury, was responsible for the disturbance. Notable was the particularly long interval between the injury and the onset of the hemiparesis, on the one hand, and the outbreak of the dystonic symptoms, on the other. The hemiparesis was present from early childhood, whereas the abnormal involuntary motor activity was not noticed before the age of 14 and became pronounced at the age of 19 years.

CASE 15.—*History.*—R. J., a white man aged 21, was born without apparent trauma, delivery being spontaneous. There were no subsequent convulsions. When he was about 8 months old weakness of his left hand and drooping of his head to the left were first noted. When he started to walk, at 3 years of age, gross weakness of the left leg was apparent; this leg also seemed somewhat stiff, and he walked and ran in a limping fashion. At about 11 years of age, without a history of preceding trauma of the head or infection, the patient began to have involuntary movements of his left arm, which gradually became more severe. At 12 years of age he began to have involuntary movements in the left leg also. At 14 years of age he became bedridden. During the two years preceding admission to the hospital he had an occasional sensation of tightness of the right lower extremity, associated with clonic movements of the right hand and arm.

The family history did not reveal a hereditary tendency.

Examination.—General examination revealed nothing abnormal except for the motor incapacity and the involuntary movements. He could not stand erect, even when aided. The head drooped forward as he slumped in an attempt to sit erect. The muscles of the right arm and leg showed increased resistance to passive movements. There was weakness of the left arm and leg, most noticeable in the dorsiflexor muscles of the wrist and fingers. Speech was fairly good, although a bit scanning and high pitched when he was excited. The deep reflexes were slightly more active in the upper and lower extremities on the right side than on the left. The abdominal reflexes were absent on the left side. The Hoffmann sign was elicited on the right, but there was no Babinski sign. The cranial nerves were normal except for myopia of 6 D. and a few ill sustained nystagmoid jerks on lateral gaze.

The results of laboratory examinations were noncontributory.

The mental status was normal.

Operation.—A cervical laminectomy was performed. The left anterior funiculus of the cord was cauterized between the second and the third cervical segment.

Film Analysis.—The patient was lying on the floor (fig. 18 *A*). The head was hyperextended and turned to the right. The left arm was adducted and flexed at the elbow and the wrist. The right arm was abducted at the shoulder, extremely flexed at the elbow and slightly flexed at the wrist. The left leg was rotated inward. The right leg was slightly flexed at the knee, and the right foot was extremely supinated and dorsiflexed, with extension of the toes.

This position was maintained for a time. Suddenly a severe attack of hyperkinesis started. The head and the right arm remained in the same position. The left arm made throwing movements as a whole, while the forearm, flexed at the elbow, swung around in wide, irregular, circling movements. The left hand was held with the fingers extended but was flexed at the metacarpophalangeal joints, and the thumb was adducted.

Waves of involuntary movements started at the same time in the trunk, later affecting the pelvis and the left lower extremity. After strong hyperextension of

the trunk (fig. 18 *B* and *C*), there occurred twisting movements of the pelvic portion (alternately to the left and to the right) (fig. 18 *D*), flexion and extension, mixed with rotation, of the leg, and, finally, complex movements of the trunk and the left thigh and leg which resembled kicking (fig. 18 *E* and *F*). The right lower extremity was constantly flexed at the knee and was only passively moved by the movements of the trunk.

Such an attack of involuntary movements took only a few seconds. Afterward the patient lay completely quiet, only an alternating tremor of the right hand and fingers persisting. This tremor was present during some attacks also.

After operation the posture was the same as before. The antagonist tremor of the right hand was not influenced. The involuntary movements during the attacks did not show any change. Perhaps the duration of the attacks was shorter.

The outstanding feature of the intricate hyperkinesis in this case was the occurrence in attacks of a storm of involuntary movements. Between these attacks the patient lay relatively quiet. Only antagonist tremor of the right hand was present, and slight changes in the position of the trunk and extremities were noticeable. At irregular intervals a wave of wormlike movements moved swiftly down the trunk, associated with throwing, flail-like movements of the left arm and alternating kicking movements of the lower extremities. There were some slow, athetotic movements of the left hand and fingers, and the alternating tremor of the right hand persisted during some attacks. There was a gradual increase in intensity of the hyperkinesis up to the height of the attack; then in a few seconds the storm gradually subsided. The attacks came on

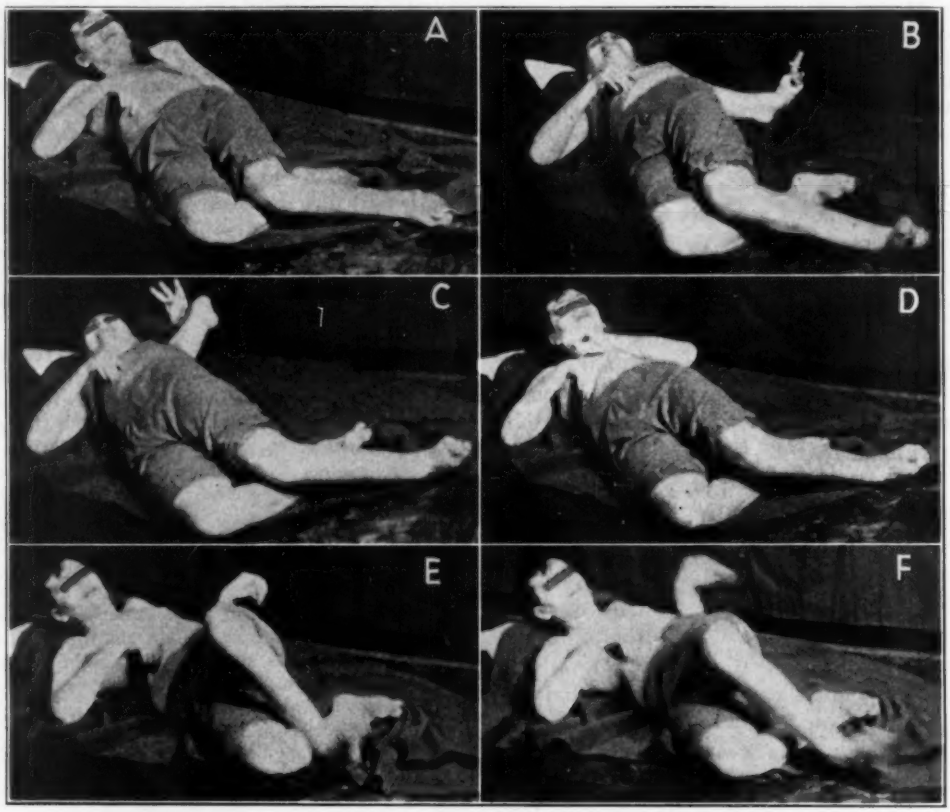

Fig. 18 (case 15).—More complicated throwing and kicking movements, in addition to dystonic movements and postures.

After spontaneous delivery, disturbances were not noticed until the child was 8 months old, when weakness of the left arm became apparent. At the time he began to walk considerable spastic hemiparesis of the left side existed. At the age of 11 or 12 years involuntary movements of the left side began and progressed rapidly. A few years later the right side, too, showed stiffness and involuntary movements.

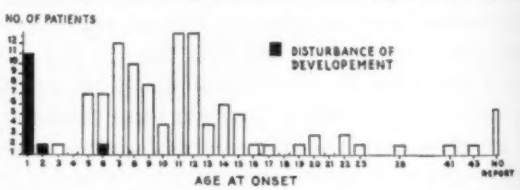

Fig. 19.—Age distribution at onset of first symptoms.

without any recognizable reason at rather irregular intervals. There was no loss or change of consciousness during the attack.

Neurologic examination revealed evidences of damage of the pyramidal tract on both sides, nystagmoid jerks on lateral gaze and considerable paresis of the left arm and leg.

The symptoms differed considerably from those in the preceding cases. Hyperkinetic attacks alternated with states of relative rest. During the latter, there were present only alternating tremor of the right hand and positions resembling dystonic postures, together with hemiparesis and signs of defect in the pyramidal tract on both sides. During the attack a more complicated pattern of involuntary movements was predominant. Twisting and turning movements of the head, trunk and arms were mixed with mass movements resembling complicated acts, such as rolling around or kicking. The mechanism of some of these movements was similar to that of athetotic and dystonic movements, but others showed a pattern resembling that of purposive movements.

From the clinical data alone one cannot classify this disease, which was presumably present at birth, with one of the known disease entities. At any rate, it should not be included with the dystonias.

The anterolateral chordotomy was without notable effect.

SUMMARY OF CLINICAL OBSERVATIONS

Common to all the cases was the occurrence of dystonic symptoms of the kind described as dystonic movements and postures in the first paper in this series.[1] The predominance of these motor symptoms in almost all cases induced the observers to suggest the diagnosis of dystonia. But after consideration of all available clinical data one may proceed to define better circumscribed clinical groups.

In the first 4 cases the significant clinical data are similar. After a normal delivery and an uneventful development during the first years of life, dystonic symptoms gradually appeared, between the ages of 8 and 13 years, and steadily progressed in severity. No apparent cause for the cerebral disorder could be found. The abnormal involuntary motor activity was the only disorder of the disease. One may, therefore, speak of a selective systemic symptomatology.

Cases 7 and 8 differed only slightly from the first cases. Dystonic symptoms constituted, again, the only feature of a disease which developed gradually in completely healthy persons. Significant are the onset of the first symptoms at a later age (18 and 23 years) and the particularly slow progress of the disease to involve circumscribed portions of the body. In case 8, in which the onset was at the age of 23, dystonic symptoms were present only in the muscles of the neck, shoulder and trunk; in case 7 in which onset was at the age of 18, dystonic tensions in the muscles of the thigh and back progressed so slightly that they usually were noticed only by the patient herself. In case 6 an earlier onset, with a feeling of tightness in one arm, was reported. Not before the age of 15 were motor disorders noticed, and then they progressed slowly. Many years later they were confined to the neck, trunk and arms.

In cases 9, 10 and 11 also dystonic symptoms were the only symptom of the disease, but they had been present since early life. Although some disturbances were observed after delivery (underdevelopment and cyanosis in case 9; convulsions in cases 10 and 11), birth injury does not seem to have been the cause of the cerebral lesion. The degree of progression in these cases was remarkably severe; in cases 9 and 11 the patients' conditions were the most pitiful in this series.

The disorder in case 5 consisted also exclusively of dystonic symptoms. They gradually developed from the age of 10 years and progressed relatively slowly. But, unlike the state in cases 1 and 4, early physical and mental development was rather slow, and the latter apparently was incomplete. One must, therefore, assume that the nervous system was somewhat subnormal at birth and, in addition, that a progressive process existed at the age of 10 years.

With respect to symptoms, development and etiologic considerations, cases 1 to 11 were similar. Without a recognizable etiologic agent, selective systemic motor disorders developed. Only dystonic symptoms were present, without other neurologic signs. These movements gradually developed, progressing and spreading over the whole body, or only over some areas.

Although I am aware that these statements are corroborated by clinical evidence alone, I suggest that the symptoms described be taken as characteristic of the dystonia group. This group consists of 4 cases of the juvenile form, with the onset of the disease between the ages of 8 and 13 years, and 3 cases of the late form, with the onset after the age of 15 years. In these 7 cases no disturbance of early development was observed. In 3 cases of early onset the motor disorder started shortly after delivery, and one must assume that the basic cerebral process was already present at birth. With respect to the onset of the disease 1 case belonged to the juvenile form, but early disturbance of development suggests the existence of an abnormality of the brain at birth.

TABLE 1.—*Cases with Dystonic Symptoms Reported in the Literature* *

Case No.	Year of Report	Author	Sex	Delivery	Development	Age of Onset, Yr.	Familial Occurrence	Group	Diagnosis
1	1893	Gowers	M	..	..	9	One brother with same disease	A	"Tetanoid chorea"
2	1901	Desterac	F	+	+	?	.....	A (probably D)	Spasmodic torticollis
3	1908	Schwalbe	1 F	..	+	11	Same family	D	Tonic spasm with hysterical symptoms
4			2 M	..	..	12		D	
5			3 ?	..	+	14		D	
6	1911	Ziehen	F	..	+	7	.....	D	Tonic torsion neurosis
7	1911	Oppenheim	1 F	+	+	9	.....	D	Dystonia musculorum deformans; dysbasia lordotica progressiva
8			2 F	+	+	12	.....	D	
9			3 M	+	+	14	.....	D	
10			4 ?	+	+	12	.....	D	
11	1911	Flatau and Sterling	1 M	..	..	7	.....	D	Progressive torsion spasm in children
12			2 M	+	+	11	.....	D	
13	1911	Higier	F	..	..	19	.....	A	Tonic-clonic movements
14	1912	Fränkel	1 M	+ (Forceps)	+	11	.....	D	Tortipelvis
15			2 M	+	+	19	.....	D	
16			3 M	+	+	10	.....	D	
17			4 M	+	Injury, convulsions —	..	.....	A	
18	1912	Bregman	1 M	..	..	16	.....	D	Spasmodic condition, juvenile form
19			2 M	..	..	18	.....	A	
20			3 M	..	..	14	.....	D	
21	1912	Bernstein	M	..	..	12	One brother with same disease	D	Torsion cramp
22	1913	Abrahamson	F	+	+	8	.....	D	Dystonia musculorum deformans
23	1913	Bonhoeffer	M	..	..	?	.....	D	Torsion spasm
24	1913	Bregman	F	..	..	8	.....	D	
25	1913	Spiller	M	..	—	Middle age	Two feebleminded sisters with chorea	A	Dystonia musculorum deformans
26	1914	Beling	F	+	+	7	.....	D	Dystonia musculorum deformans
27	1914	Haenisch	M	..	..	?	.....	A	Progressive torsion spasm
28	1914	Kroll	M	..	—	Postpartum onset	.....	D	Double athetosis
29	1914	Seelert	M	+	+	6	.....	D	Progressive torsion spasm
30	1915	Biach	M	..	..	15	.....	D	Dystonia musculorum deformans
31	1915	Climenko	F	+	+	9	.....	D	Dystonia musculorum deformans
32	1916	Sterling	M	..	..	14	.....	D	
33	1916	Diller and Wright	M	..	..	Before age of 14	.....	D	Dystonia musculorum deformans
34	1916	Patrick	1 M	..	..	Middle age	.....	A	Dystonia musculorum deformans
35			2 M	..	..	?	.....	A	
36			3 M	..	..	?	.....	A	
37	1916	Hunt	1 M	..	..	8	.....	D	Progressive torsion spasm of childhood
38			2 M	+	+	6	.....	D	
39			3 M	..	..	9	.....	D	
40			4 F	..	..	10	.....	D	
41			5 F	..	..	11	.....	D	
42			6 F	..	..	17	.....	D	
43	1917	Weisenburg	M	+	+	6	.....	D	Unusual torsion spasm
44	1917	Dercum	M	+	+	19	.....	A	Anomalous torsion spasm
45	1917	Hallock and Frink	F	+	+	5	.....	D	Dystonia musculorum deformans
46	1918	Keschner	F	+	+	12	.....	D	Dystonia musculorum deformans
47	1918	Kramer	M	..	..	47	.....	B	Torsion spasm in adult
48	1918	Thomalla	M	+	+	13	.....	B	Torsion spasm
49	1919	Mendel	1 M	+	+	13	.....	D	Torsion dystonia
50			2 F	+	+	5	.....	D	
51	1920	Frauenthal and Rosenheck	F	+	+	7	.....	D	Dystonia musculorum deformans
52	1920	Abrahamson	1 F	+	+	12	Same family	D	Familial dystonia of Oppenheim
53			2 F	..	..	?	(brother and	D	
54			3 M	..	..	?	2 sisters)	D	
55	1920	Taylor	1 M	+	+	7	Same family	D	Dystonia lenticularis
56			2 F	+	+	7	(brother and sister)	A	Dystonia musculorum deformans
57	1920	Collier (Blandy)	M	+	+	5	Sister with infectious chorea	D	Torsion dystonia
58	1920	Spiller	F	..	+	5	.....	D	Acquired double athetosis; dystonia lenticularis
59	1921	Dawidenkow and Zolotowa	M	..	..	13	One sister and one daughter with same disease	A	Dystonia musculorum deformans
60	1921	Price	1 M			3	Twins	A	Dystonia lenticularis in twins
61			2 M			..	.....	A	

* In this table, the plus sign indicates normal delivery or development; the minus sign, abnormal delivery or development, and .. no data.

TABLE 1.—*Cases with Dystonic Symptoms Reported in the Literature—Continued*

Case No.	Year of Report	Author	Sex	Delivery	Development	Age of Onset, Yr.	Familial Occurrence	Group	Diagnosis
62	1922	Patrick	M	+	—	6	Other twin died of cerebellar glioma	D	Dystonia musculorum deformans
63	1922	Yawger	?	—	—	Postpartum onset		D	Dystonia musculorum deformans
64	1921	Wimmer	F	—	—	10		B	Progressive torsion spasm, infantile form
65	1921	Flater	F	..	—	8		D	Torsion dystonia
66	1922	Wartenberg	M	..	..	Puberty		D	Torsion dystonia
67	1922	Fossey	F	..	..	23	Six relatives with chorea; 1 brother with dystonia	B	Dsytonia musculorum deformans
68	1922	Wechsler and Brock	1 M	..	..	11		D	Dystonia musculorum deformans
69			2 M	..	..	8		D	
70			3 F	..	..	12	Four others with	D	
71			4 M	..	..	11	disease in family	D	
72			5 M	..	..	?		D	
73			6 F	..	..	8		D	
74	1922	Jacob	M	..	—	12		D	
75	1922	Rosenthal	1 F	..	—	12		D	Torsion dystonia
76			2 M	—	—	6		D	
				8 mo. child					
77	1922	Cassirer	1 M	..	..	41		D	Torticollis and torsion spasm; dystonia musculorum deformans
78			2 M	..	—	7		D	
79	1922	Ewald	M	—	—	9		D	Torsion dystonia
80	1922	Pollock	F	..	..	43		D	Dystonia
81	1923	Rosenthal	1 M	—	—	10		A	Cerebral disease at early age
82			2 F	—	—	7		D	
83	1923	Margaretten	F	—	—	2 wk. postpartum		D	Dystonia with athetoid features
84	1923	Solomon	1 ?	..	..	?		A	Dystonia lenticularis
85			2 ?	..	..	?		A	
86	1923	Wartenberg	M	+	+	11		D	Torsion dystonia
87	1923	Richter	F	+	+	11		D	Torsion dystonia
88	1924	Fraenkel	1 F	..	..	40		B	Dystonic syndrome
89			2 F	..	..	12		D	Torsion dystonia
90	1924	Prissmann	M	+	+	8		D	Torsion dystonia
91	1926	Itzenko				..		A	
92	1925	Stertz	M	..	+	7		D	Torsion spasm
93	1925	Urechia, Mihalescu and Elekes	M	+	+	6		B	Dystonia lenticularis
94	1925	Moser	1 F	..	+	11		D	Organic torticollis
95			2 F	..	+	23		D	
96	1926	Roussy and Levy	F	..	..	60		B	Torsion spasm
97	1926-1927	Marotta	1 M	+	+	7		D	Torsion dystonia
98			2 M	+	+	11		B	
99			3 M	+	—	Postpartum onset		D	
100			4 M	+	..	7		B	
101	1927	Heuyer and Badonnel	F	..	..	9		A	Torsion spasm
102	1927	Chavany and Morlaas	F	..	..	17		B	Torsion spasm
103	1927	Navarro and Marotta	M			..		A	
104	1927	Chiari	M			..		B	Hemilateral torsion spasm
105	1928	Austregesilo and Marques	1 F	—	—	7 mo.		D	Dystonia
106			2 M	..	+	13		A	
107			3 M	—	—	..		A	
108	1928	Kleist and Herz	1 M	—	—	Postpartum onset		A	Congenital defect
109			2 M	+	+	22		D	Torsion dystonia
110	1928	Marotta	F	..	..	4		A	Torsion dystonia
111	1929	Zolotova	1	—	—	Postpartum onset		D	Torsion syndrome in children
112			2	—	—	..		D	
113	1929	Marinesco and Nicolesco	F	..	+	15		D	Spasmodic contorsional dystonia
114	1929	Roasenda	1 F	..	..	40		B	Torsion spasm
115			2 F	..	..	40		B	
116			3 M	..	..	28		B	
117	1929	Laruelle and van Bogaert	?	..	—	Postpartum onset		D	Syndrome of rigidity with torsion spasm
118	1929	Bouman	M	+ (forceps)	+	5		D	Torsion spasm
119	1929	Laruelle	M	—	+	12		D	Torsion spasm
120	1929	Léri, Layani and Weill	F	+	+	3		D	Dystonia
121	1929	Mankowsky and Czerny	1 M	..	..	7	Congenital cardiac defect in family: 1 sister with same disease as patient	D	Torsion dystonia
122			2 F	..	..	8	Brother of preceding patient	D	

TABLE 1.—*Cases with Dystonic Symptoms Reported in the Literature—Continued*

Case No.	Year of Report	Author	Sex	Delivery	Development	Age of Onset, Yr.	Familial Occurrence	Group	Diagnosis
123-137	1929	Brzezicki				..		A	Torsion dystonia
138	1930	Lafora	M			..		A	
139	1930	Stern	?	..	..	12		D	Dystonia
140	1930	Brunschweiler				..		A	Abortive torsion spasm
141	1930	Regensburg	1 M	..	+	11	Several cases in family	D	Dystonic torsion symptom complex
142			2 M	..	..	11	Nephew of first patient	D	
143	1930	von Hallervorden	?	..	..	22		B	Athetosis with symptoms of torsion spasm
144-148	1930	Fracassi and Marelli				..		A	Torsion spasm
149	1930	Cudnow	?	..	..	13		A	Torsion spasm
150	1931	Seidemann	F	..	+	2		A	Torsion spasm
151	1931	Luethy (case 3 of Jakob [1932])	?	..	..	18		B	Hepatolenticular degeneration
152	1931	Dias (case 2 of Jakob [1932])	F	..	.. Debility	10		B	Torsion dystonia
153	1931	Ramos Fernández	1 M	..	..	15		D	Torsion spasm
154			2 ?	—	—	Post partum		A	
155	1931	Vizioli	?	+ Premature	..	?		B	Torsion spasm
156	1932	Jakob	1 M 2 [Dias] 3 [Luethy]	..	..	15		D	Torsion spasm
157	1932	Garland	M	..	+	5		A	Torsion spasm; dystonia lenticularis
158	1932	Budde	?	..	..	6		D	Torsion dystonia
159	1932	Schmitt and Scholz	M	..	+	22		D	Torsion dystonia
160	1932	Dubitscher	?	+	+	6		B	Hyperkinetic-dystonic syndrome
161	1932	Laruelle and Divry	F	..	+	31		A	Torsion spasm
162	1932	Rakonitz	F	..	..	23		A	Exogenous unilateral torsion dystonia
163	1932	Saegesser	F	..	..	28		D	Torticollis spastica
164	1933	Foerster	M	..	..	20		D	Torticollis
165	1933	Noble de Mello and Quintanilha	M	..	..	33		B	Dystonia
166	1934	Quadfasel and Krayenbühl	M	..	..	15		D	Torticollis spastica
167	1934	Santangelo	1 F	..	..	9	Three sisters with disease	D	Dysbasia lordotica, familial type
168			2 F	..	..	9		D	
169			3 F	..	..	9		D	
170	1934	Agostini	F	..	..	10		B	Torsion spasm
171	1936	Zádor	M	+	+	10		D	Torsion spasm
172	1935	Beilin	M	+	+	11		D	Torsion syndrome
173	1935	Munch-Petersen	M	..	+	18		A	Torsion dystonia
174	1937	Paulian and Cardas	1 F	..	..	33		B	Torsion spasm
175			2 M	..	..	35		A	
176			3 M	..	..	8		A	
177			4 M	..	..	5		A	
178			5 M	..	..	5		D	
179	1938	Davison and Goodhart	1 F	..	—	6 wk. post partum		D	Dystonia musculorum deformans
180			2 F	..	+	14		D	
181			3 M	..	+	8		D	
182			4 M	..	+	7		D	
183	1938	Maspes and Romero	M			..		A	Torsion spasm with athetosis
184	1939	Gordin	M	..	+	22		A	Unilateral torsion dystonia
185	1940	Benedek and Rakonitz	1 F	..	—	Post-partum onset		D	Myoclonic torsion dystonia
186			2 F	..	..	Child-hood	Mother of first patient and brother of first patient	A	
187			3 M	..	+	..		A	
188	1941	Nielsen	M	+	—	18 mo.		D	Dystonia musculorum deformans

The clinical data common to the first 11 cases are in such definite contrast to the data for the last 4 cases that the latter should be classified separately. In case 14 hemiparesis was combined with unilateral dystonic symptoms. The disorder was presumably due to injuries of the brain at birth, as suggested by the disturbances after delivery. In case 13 the same symptoms were presented—spastic hemiparesis with unilateral dystonic tensions. The disease came on in early childhood and did not progress. The condition was presumably due to a lesion in the brain stem of infectious or vascular origin.

In case 12, whenever dystonic symptoms appeared, there were, in addition, signs of a lesion of the pyramidal system. At the age of 2 years the patient had an acute disease of the central nervous system, and the motor disorders, starting at the same time, may have been due to the former disease. These facts being taken into consideration, classification of such cases should be postponed.

The disorder in case 15 started in early childhood and was progressive. Dystonic movements could be observed, but the occurrence of attacks of more complicated hyperkinesia did not fit in the pattern of the dystonia group. Cases with such uncommon symptoms should be separated as representing an "unknown progressive disease of early childhood with involuntary movements."

REVIEW OF CASES IN THE LITERATURE

To supplement and test this clinical material and the aspects of the classification outlined, all the cases reported in the literature were reviewed and the clinical data reexamined. In table 1 are presented the data on 188 cases with symptoms of dystonia published since the first detailed description by Schwalbe.

Of these 188 cases, the given or available data for 61 cases did not seem adequate for diagnostic consideration. (These cases are designated as group A.) In another 22 cases the clinical signs and symptoms, and in some instances the pathologic picture after anatomic investigation, leave no doubt that they must be classified under other, well known disease entities. (These cases are designated as group B.) This group contains 4 cases of Huntington's chorea (chronic progressive chorea); 4 cases of Wilson's disease (hepatolenticular degeneration); 11 cases of chronic epidemic encephalitis; 2 cases in which there were vascular lesions, and 1 case of Hallervorden-Spatz disease. After elimination of groups A and B, 105 of the 188 cases remain. (These cases form group D.) They must be assigned to the preliminary "dystonia group," as previously outlined. A more or less progressive disease developed without known cause. During the entire course, involuntary motor activity in the form of dystonic movements and postures characterized the disturbance; no other disorders were revealed by neurologic examination. The three groups may be summarized as follows:

		No. of Cases
Group A	Report available incomplete or diagnosis unconfirmed	61
Group B	Condition classifiable with other well known diseases	22
Group D	Dystonia	105
	Total	188

Table 2 and figure 19 show the age distribution for cases of the dystonia group at the onset of the first symptoms. In 10 cases, or 9.5 per cent, the disease appeared immediately after the delivery or in the first few weeks of life (early form). In the majority of cases, 78, or 74.3 per cent, the onset of the disease was between the ages of 5 and 15 years (juvenile form). In a third, much smaller, group the first symptoms started at a more advanced age (late form).

All reports were carefully examined with respect to disturbances during and after delivery and retardation of development. Instrumental delivery was regarded as significant only if objective signs observed immediately post partum indicated the presence of impairment of the nervous system. As can be seen from table 3, both the delivery and the development were reported to be normal in 34 cases. In 18 additional cases the development was normal, but no exact information on the delivery was given. Thus, in 52 of 105 cases (49.5 per cent) there was certain normal development until the onset of the first symptoms of the disease. After normal delivery, retardation of development was seen in 4 cases; both disorders after delivery and retardation of development were present in 4 cases, and retardation of development without any report on delivery was noted in 4 cases. Altogether, in 12 of 105 cases (11.5 per cent) there was retardation of development. Only in 1 case were there disorders shortly after birth and later normal development. In 40 cases no report on delivery or development was given. In summary, development was normal until the onset of the first symptoms in 52 cases (49.5 per cent) and was retarded in 12 cases (11.5 per cent). In only 2 cases of the infantile form was there retardation of development, whereas it was present, of course, in all cases of the early form, in

TABLE 2.—*Age Distribution at Onset of First Symptoms*

Form	No. of Cases	Percentage
Early	10	9.5
Juvenile	78	74.3
Late	11	10.0
Total number of cases in which age was reported at onset of disease	99	

TABLE 3.—*History of Delivery and Development in One Hundred and Five Cases*

Delivery normal; development normal	34	52 (49.5%)	Normal development
No exact report on delivery; development normal	18		
No exact report on delivery or development	40	39.0%	
Delivery with disorders; development normal	1		
Delivery normal; development incomplete	4	12 (11.5%)	Incomplete development
Delivery with disorders; development incomplete	4		
No report on delivery; development incomplete	4		

which the motor disturbances started shortly after birth.

The symptoms in the reported cases were studied carefully in order to find differences in the three groups. In most cases of early onset involuntary movements seemed to prevail over dystonic postures and long-sustained lesions. But in other cases of early onset, e. g., in case 9 of the present series, particularly significant dystonic tensions and postures were presented. As a matter of fact, from the symptoms alone, without knowledge of the history of the development of the disease, it is not possible to state the time of the onset of the disease in the majority of cases.

Frequently, in cases of late onset only torticollis was presented at the onset of the disease. Dystonic movements and tensions of the neck and shoulders appeared first; later, the trunk and extremities became involved. Only cases in which there was progression of involuntary movements and tensions from the head to other parts of the body are considered in this paper. The problems connected with pure torticollis will be analyzed separately. It may only be mentioned that the disorder in the cases of pure torticollis begins predominantly, or perhaps exclusively, at a later age, so that the number of cases of late-appearing dystonia could be considerably increased by inclusion of the cases of torticollis.

The predominant occurrence of dystonia in families of Russian Jewish descent was striking in the first observations on this disease. Later, cases which did not belong in this racial group were described, and in the last ten years instances of dystonia have been found in the population of almost all countries of the world, without respect to race. I have not elaborated on the possible prevalence of dystonia in any one group. Similar observations on other diseases of unknown origin (e. g., infantile amaurotic familial idiocy, or Tay-Sachs disease) had to be taken as fact. On the other hand, recent experiences with *Rassebiologie* have been so depressing and grotesque that they do not encourage speculations.

Familial occurrence has been reported only in 8 instances. In the cases of Schwalbe (1908), Bernstein (1912), Abrahamson (1920), Wechsler and Brock (1922), Mankowsky and Czerny (1929), Regensburg (1930), Santangelo (1934) and Beilin (1935), several members of the same family had dystonia. Patrick (1921) described a twin with this disease; his twin brother died of a cerebellar glioma. The character of the disease of the twins reported on by Price is not clear. The occurrence of convulsions and optic nerve atrophy does not make the diagnosis of dystonia probable. Kehrer, in his analysis of the *Erblichkeitskreis* of torsion dystonia, did not consider in sufficient detail the difference in genesis and origin. His own case of "progressive torsion dystonia with idiocy and retinitis pigmentosa" surely does not belong with the cases of dystonia. The largest number of diseased members in the same family was reported by Regensburg, who concluded that there was "an exquisitely hereditary, or familial, character in a series of cases." But from his description the diagnosis of dystonia appears doubtful for some members of the family. My own experience leads me to agree rather with Mendel (1936) that hereditary factors are not traceable in the majority of cases of dystonia.

CONCLUSIONS

1. Dystonic movements and dystonic postures are symptoms of an organic nervous disease. Their occurrence alone does not enable one to make the diagnosis of a disease entity.

2. On the basis of all the available clinical data, the clinician is able to separate cases which are classifiable under well known diseases, such as chronic epidemic encephalitis, Wilson's disease and Huntington's chorea. Neither these cases nor other cases in which appear gross lesions of known character, such as tumor, vascular lesions and birth injuries, should be included with the dystonias.

3. The diagnosis of "dystonia" should be made only in cases with the following clinical characteristics: (*a*) selective systemic symptoms in the form of dystonic movements and postures, and (*b*) gradual development, without recognizable etiologic factors at the onset.

4. The dystonias may be further classified into the early form, with an onset at or shortly after birth; the juvenile form, with an onset between the age of 5 and 15 years, and the late form, with an onset after the age of 15.

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DELIRIUM

I. ELECTROENCEPHALOGRAPHIC DATA

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CINCINNATI

Delirium is a term of many meanings. Literally it means "to go out of the furrow in ploughing," i. e., "to go off the track." We shall use it to describe a syndrome sometimes called the symptomatic psychosis, the toxic-infectious exhaustion state or psychosis associated with somatic disease. Essentially it is a more or less reversible psychotic episode appearing symptomatically during the course of an underlying physical disorder. Thus, it may occur in patients with no preexisting structural cerebral disease and may be associated with such conditions as drug intoxications, febrile states and cardiac and renal disease. It may also occur spontaneously or may be precipitated by the aforementioned factors in patients with preexisting structural cerebral disease.

Previous psychologic and clinical studies [1] have led us to formulate a principle of release for the explanation of the intellectual, emotional and motor regressive behavior of delirious patients. We have found the primary psychologic disturbance to be that of an increased fluctuation in the level of awareness. Further, we have accumulated data to illustrate the loss of ability to think in the abstract. In experimental and spontaneous situations, the emotional behavior of patients has been more understandable when interpreted in the light of a release of inhibiting or repressing factors. Similarly, the purposeless body movements have been interpreted as due to a release of higher cerebral function and a return of behavior to a lower order of integration. These observations have led us to consider the fundamental physiologic substratum of delirium. If the total behavior of the delirious patient may be interpreted as due to a release from higher cerebral function, what evidence other than clinical and psychologic data may be presented to support such a hypothesis?

The sensitive metabolic needs of cerebral tissue, particularly of the cortex, are well known. Serious disturbances in functional integrity of the cortex seem likely in the course of the physiologic derangements associated with physical disease. These physiologic derangements may result ultimately in (1) disturbances of transportation of oxygen, dextrose and other essential foodstuffs to the brain or (2) an alteration of the essential intracellular integrity and metabolism of the brain or (3) a combination of the two.

Methods of study of cortical function in human beings are limited, but knowledge based on animal experimentation that the electrical activity of nerve tissue closely parallels its functional integrity opens the possibility of a similar approach to the study of the human cortex. The electroencephalograph offers a method of study of the electrical activity of the human cortex. Gerard and associates [2] have presented evidence to show that the electroencephalogram represents the synchronized electrical activity of the individual neurons. Major factors determining these neuron potentials are the metabolic status of the cell, the membrane charge and the nature of the surrounding fluid medium. They may be modified, but are not solely determined, by influent nerve impulses. Changes in the rate, form and, within limits, amplitude induced by applied agents may be interpreted in terms of the individual neuron beat. Regularity, on the other hand, may be more readily interpreted in terms of synchronization. There is further evidence to suggest that this synchrony may be controlled or enhanced by "pace-making" cells, which set off other cells. In human beings and in animals

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striking changes in the electroencephalogram resulting from anoxia, hypoglycemia, acapnia, alkalosis and electrolytic imbalance have been demonstrated.[3] Other investigations have clarified the effects of drugs which alter consciousness.[4] Clinically a number of studies of the electroencephalographic changes in patients with diffuse inflammatory, traumatic or degenerative diseases of the brain [5] have been carried out. In addition, there are reports of electroencephalographic changes in patients with disease not directly affecting the central nervous system, such as Addison's disease and pulmonary and cardiac insufficiency.[6] Unfortunately, in many of these clinical studies the psychologic data, even as they related to the level of consciousness, are incomplete.

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METHODS

A. *Psychologic Methods.*—A detailed report of the intellectual and emotional behavior of delirious patients will be found in another report.[1b] In this paper we shall enumerate the psychologic methods used principally to determine the fundamental psychologic disturbance, i. e., the increased fluctuation of the level of awareness.

After a traditional examination of the mental status was completed, with particular attention to the sensorium, each patient was presented with an additional battery of clinical psychologic tests. These included:

1. Tests for attention
   (*a*) Number and letter series
   (*b*) Serial subtraction
2. Tests of memory
   (*a*) Five objects test
   (*b*) Retention of digits, forward and backward
   (*c*) Syllable span
   (*d*) Fire story
   (*e*) Word pairs
   (*f*) Story recall (confabulation)
3. Arithmetical tests
4. Tests of capacitly for abstract thinking
   (*a*) Group arrangement
   (*b*) Goldstein (Kohs) blocks
   (*c*) Proverbs and fables

With this method of examination we encountered a significant number of patients in the medical wards who fulfilled the essential criteria of delirium as defined by us but who had not been recognized as delirious by the medical attendants. The disturbance of awareness in these patients was demonstrated chiefly by testing, as many did not spontaneously express the anxiety, motor restlessness, disturbed thinking and sense deceptions characteristic of the more obviously disturbed patients. These patients were not necessarily experiencing milder degrees of delirium. On the contrary, such patients were apt to become somnolent and stuporous without a preceding phase of excitement.

The tests were repeated from time to time during the course of the delirium. It is to be noted that the limitations of the methods used were understood by us and were employed to indicate changes of clinical significance. The changes observed could not be explained by the patient's having learned the material, as the disturbance in memory and the magnitude of changes made this unlikely.

For gross comparison the disturbances in awareness were classified as mild, moderate and pronounced. With mild disturbance in the level of awareness the patient was generally correctly oriented but tended to make errors in serial subtraction and in the arithmetical tests, manifested memory defects and generally had some difficulty in abstract thinking. With a moderate disturbance the subject revealed some errors in orientation and gross errors in attention, memory and capacity for abstract thinking, but usually was able more or less to complete the tests. The disturbance was classified as pronounced when the patient had great difficulty in comprehending the nature of the examination and could not sustain attention. Such patients usually were disoriented to a conspicuous degree and were unable to complete the tests. Overactivity, as

manifested by sense deceptions, confabulation and motor restlessness, and underactivity, including somnolence and stupor, were common features of patients with severe disturbances.

B. *Electroencephalographic Methods.*—Electroencephalograms were taken each time the patient was studied psychologically. A two channel,[7] and later a three channel, ink-writing apparatus, constructed by Mr. Albert Grass, was used. Solder electrodes were placed on the frontal, parietal and occipital areas. Bipolar tracings were taken routinely from the left fronto-occipital, the right fronto-occipital, the transfrontal, the transparietal and the transoccipital leads. Other electrode combinations were used whenever indicated for exclusion of focal abnormalities. Tracings were taken from each area for a run of five minutes. Every precaution was observed to avoid the artefacts of sleep or movement. It is our belief that artefacts occur less frequently when the bipolar method is used. This is of practical importance in the study of disturbed patients. The patients were under constant surveillance of the operator, so that any movement could be recorded. Occasionally simultaneous records of eyeball potentials were taken to exclude movement of the eyes as a source of artefact.[8]

In the interpretation of the electroencephalogram, particular attention was directed to the progressive changes which occurred during the clinical course. The chief features considered were (1) frequency, (2) amplitude, (3) regularity and degree of organization, (4) paroxysmal features, (5) focal abnormalities and (6) wave form.

In order to demonstrate these progressive changes more quantitatively, a method of spectrum frequency analysis was devised. Frequency was selected as the variable for analysis, since data previously cited[2] have indicated that it is probably the most valuable index of the activity of individual neurons as influenced by such factors as metabolic states, membrane charge and nature of the surrounding mediums.

The method is described in detail elsewhere.[9] Briefly, it involved counting the number of waves in each one second interval for a total of three hundred seconds. A complete wave is one which returns at least 60 per cent of the way to the base line. For practical purposes it was found that the countable waves ranged in frequency from 1 to 12 per second, while the faster waves existed largely as low voltage irregular waves, which could not be accurately counted and hence were grouped together as low voltage fast activity. Low voltage fast waves superimposed on discrete, countable (1 to 12 per second) waves were ignored. When a given interval contained both countable waves and low voltage fast activity, the frequency which occupied the greater portion of that interval was arbitrarily taken as dominant.

Such an analysis yields a "spectrum" expressing the distribution of waves for one second intervals rather than that of true wavelengths—that is, the percentage of one second intervals containing 12 waves, 11 waves, etc., rather than the percentage of 12 per second waves, 11 per second waves, etc. It is obvious that sporadic waves faster or slower than the dominant frequency will be averaged with the more dominant frequency and hence will not be represented in the spectrum, although they may be obvious on inspection; this, however, does not obscure shifts in frequency, detection of which is the primary objective of the method.

With very regular records the error in this method is relatively insignificant. Under the same conditions, a rather consistently reproducible frequency spectrum can be obtained.[9] Observations on normal adults indicate that the normal records may be classified under two chief types, i. e., (1) records with 75 per cent or more 8 to 12 per second activity, with the remainder low voltage fast activity, and (2) predominantly low voltage fast activity, with small and varying amounts of 8 to 12 per second activity. It is unusual in our experience to find that a normal record contains more than 5 per cent 7 per second activity. Minimal variations in the dextrose, oxygen and carbon dioxide contents have been found to produce significant alterations in the frequency distributions of normal records.[9] With abnormal records, as the degree of irregularity increases, this method of analysis becomes less accurate, but for comparative purposes the error is more or less self limited, since the more irregular records are generally the more abnormal and the frequencies tend to shift to a large degree to the abnormally slow or the abnormally fast zones.

Spectrum analyses were performed at each examination. The left fronto-occipital tracing was utilized routinely unless focal differences were present. We utilized the fronto-occipital tracing because it represented a composite of the electrical activity of the major portion of the hemisphere. We were interested in examining the grosser features of cortical activity before embarking on a more detailed study of discrete cortical areas.

C. *Special Physiologic Studies.*—The routine laboratory tests pertinent to each patient's problem were carried out. In addition, certain special procedures were utilized. For patients with cardiac or pulmonary decompensation, the venous pressure, the circulation time (dehydrocholic acid), the vital capacity and the oxygen saturation of arterial blood were determined. Dextrose tolerance tests (0.5 Gm. of dextrose per kilogram of body weight introduced intravenously in 10 per cent solution in thirty minutes) were carried out on patients with Addison's disease and others with malnutrition associated with debility and chronic disease.

CLINICAL MATERIAL

Fifty-three patients were studied. The basic pathophysiologic factors underlying the delirious state were usually multiple, and probably cumulative, but in general the patients could be classified under the following disease categories: (1) acute or chronic cardiac decompensation, 15 patients; (2) acute or chronic pulmonary decompensation resulting from chronic asthma, bronchitis, emphysema or recurrent pneumonitis, 7 patients; (3) structural cerebral disease (atrophy, vascular degenerative changes and Sydenham's chorea [chorea minor]), 5 patients; (4) malnutrition and wasting due to chronic infection or neoplastic disease, 5 patients; (5) chronic alcoholism and delirium tremens, 5 patients, including 1 patient with Wernicke's encephalopathy (hemorrhagic superior polioencephalitis); (6) toxic states due to acute infections, 2 patients, including 1

7. Dr. Hallowell Davis loaned the two channel electroencephalograph which was used in the early experiments.

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patient with typhus (Brill's disease); (7) malignant hypertension, acute glomerulonephritis or uremia, 4 patients; (8) severe anemia, 3 patients, 2 of whom had pernicious anemia; (9) Addison's disease, 3 patients; (10) jaundice, 2 patients, the condition of 1 being due to biliary obstruction and that of the other to hepatic degeneration; (11) acidosis associated with diabetes, 1 patient, and (12) epilepsy, 1 patient.

RESULTS

Electroencephalographic abnormalities were observed in the records of all patients who had disturbances of awareness. These changes were diffuse in the tracings of all but 3 patients for whom other data confirmed focal cerebral involvement. The character of the electroencephalographic change appeared to be independent of the specific underlying disease process in all cases except those of the 3 patients with Addison's disease, which will be discussed in detail. A more significant relation was found between the electroencephalographic changes and the intensity, duration and reversibility of the noxious factors as modified by the basic physiologic status of the body, particularly that of the central nervous system prior to the experience of delirium. These changes were observed to be reversible to the extent to which the clinical delirium was reversible.

When the electroencephalograms were analyzed as a group and individually during the patient's recovery or as missing metabolic requirements were supplied, the varieties of changes were found to constitute various stages of a continuous process. For purposes of convenience we have arbitrarily classified these electroencephalographic changes under five categories: It must be emphasized that the divisions are arbitrary and that the various stages represent phases of a continuous process. They are enumerated in the order of their increasing severity (fig. 1).

Stage I: Predominance of normal and regular frequencies, but with a small amount of regular and irregular slow frequencies (5 to 7 per second). There is generally some decrease in regularity of the record as a whole.

Stage II: A further decrease in regularity of the entire record, which now contains only a moderate amount of normal, regular frequencies. There is an increase in both low voltage fast activity and regular and irregular slow (4 to 7 per second) frequencies.

Stage III: Predominant low voltage fast activity with some regular and irregular slow frequencies (3 to 6 per second) and relatively little activity of the normal frequency range.

Stage IV: Completely disorganized, irregular record, with a dominant slow frequency (2 to 7 per second), varying small amounts of low voltage fast activity and no recognizable alpha activity (8 to 12 per second). At this stage groups of high voltage very slow waves (½ to 3 per second) frequently recur in a rhythmic fashion. Low voltage fast activity is sometimes superimposed on these slow waves.

Stage V: Fairly regular, moderately high voltage slow activity (3 to 7 per second), with few or no normal frequencies.

Stages III, IV and V are not influenced by the subject's opening or closing the eyes.

As stated previously, stages I to V represent graduations of a continuous process. However, stage V represents a more or less stabilized, and often irreversible, progression from stage IV. It suggests reorganization or stabilization of the electrical pattern at a lower energy level. The correlation between the clinical course and the electroencephalographic changes may best be demonstrated by the following classification of our material.

Group I. Twelve patients showed complete, or nearly complete, restoration to normal of the clinical behavior and of the electroencephalographic pattern. The following tabulations indicate the underlying physical disease, the degree of psychologic disturbance and the stage of electroencephalographic abnormality during the period of observation.

CASE 1.—*M. R., a woman aged 28, Acute and chronic alcoholism: Wernicke's syndrome. Duration of delirium before first examination, eight days. Admission, Jan. 1, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/2	Pronounced; patient semi-stuporous	IV (fig. 4)	Parenteral administration of fluids; tube feedings; no supplemental
1/5	Pronounced; Korsakoff syndrome	IV-III	vitamins
1/7	Pronounced; Korsakoff syndrome	III	
1/12	Moderate	II	
1/16	Mild	I	
2/25	None	Normal pattern	

CASE 2.—*K. T., a woman aged 61. Hypertensive heart disease: congestive heart failure. Duration of delirium before first examination, two weeks. Admission, Dec. 16, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/29/41	Severe	IV	Circulation time 34 sec.
1/ 5/42	Moderate	II	Circulation time 20 sec; venous pressure 20 mm. of water
1/7	Mild	I	
4/17	None	Normal pattern	No congestive heart failure

CASE 3.—*H. C., a boy aged 13 yr. Acute glomerulonephritis; epilepsy (?). Duration of delirium before first examination, two days. Admission, Feb. 11, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/12	Severe	IV (fig. 3)	Two convulsions on preceding day; blood pressure 160/110; proteinuria, 4+; nonprotein nitrogen of blood 41 mg. per 100 cc.; facial edema 1+
2/16	Mild	III-II	Dramatic clinical improvement; proteinuria 2+; nonprotein nitrogen of blood 39 mg. per 100 cc.; wave and spike electroencephalographic pattern during hyperventilation
2/25	None	I*	Proteinuria 1+; wave and spike pattern still present on hyperventilation
3/13	None	I*	Proteinuria 1+; nonprotein nitrogen of blood 41 mg. per 100 cc.; wave and spike pattern still present
3/24	None	I*	Proteinuria 1+

* In this case, stage I of the electroencephalographic pattern was complicated by the paroxysmal, spontaneous appearance of slow waves, in addition to the wave and spike pattern following hyperventilation. We interpreted this as evidence of an epileptic predisposition. The clinical history tended to confirm this. During recovery, the record became progressively more regular, and the percentage of normal frequencies increased from zero to 75 per cent.

CASE 4.—*A. P., a woman aged 74. Anemia, of unknown cause. Duration of delirium before first examination unknown. Admission, April 6, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/9	Moderate	II	Hemoglobin content 2.5 Gm. per 100 cc., red blood cells 630,000 and white cells 7,000 per cu. mm.; oxygen content of arterial blood 5.3 volumes %; nonprotein nitrogen of blood 58 mg. per 100 cc.
4/11	Mild	I to normal	After transfusion of 1,000 cc. of blood, hemoglobin content 5.8 Gm. per 100 cc. and red cells 1,660,000 per cu. mm.; oxygen content of arterial blood 9.8 volumes %
5/1	Normal state	Electroencephalogram not made	After transfusion of 1,500 cc. of blood, hemoglobin content 7.2 Gm. per 100 cc. and red cells 2,010,000 per cu. mm.

CASE 5.—*E. D., a woman aged 67. Pernicious anemia; combined system disease. Duration of delirium before first examination, over three weeks. Admission, Dec. 26, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/6	Pronounced	V-IV	Hemoglobin 7.12 Gm. per 100 cc.; red cells 2,090,000 per cu. mm.; reticulocyte count 35 %; intramuscular injections of 1 cc. of liver for ten days
4/17	Mild	Normal pattern	Hemoglobin 13 Gm. per 100 cc.

CASE 6.—*J. N., a man aged 36. Diabetes mellitus, with acidosis. Duration of delirium before first examination, two days. Admission, Jan. 9, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/10	Mild	II	In preceding 16 hr. patient received 200 units insulin and 3,000 cc. of 5% dextrose in saline solution; carbon dioxide content of arterial blood 40.9 volumes %; blood sugar, 161 mg. per 100 cc.
1/12	None	I to normal	No chemical evidence of acidosis or hyperglycemia

CASE 7.—*H. O., a man aged 62. Typhus. Duration of delirium before first examination, one week. Admission, April 23, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/25	Moderate	II	Patient improving; temperature 103 F.; cerebrospinal fluid pressure 170 mm. of water; 10 white cells per cu. mm.; total protein 53 mg. per 100 cc.
4/30	None	Normal pattern	Patient afebrile 6 days; decided clinical improvement

CASE 8.—*H. H., a man aged 45. Vascular degenerative cerebral disease; carbon monoxide encephalopathy(?). Duration of delirium before first examination, five weeks. Admission, Feb. 8, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/27	Severe	V	Diagnostic problem: degenerative or inflammatory disease (?)
3/9	Mild to None	I	Patient gradually improved; residual weakness on right side; rigidity; tremor

CASE 9.—*E. M., a woman aged 47. Epilepsy; diphenylhydantoin intoxication (?). Duration of delirium before first examination unknown. Admission, Feb. 26, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/28 10:30 a. m.	Moderate to mild	II (fig. 2)	Psychomotor seizure at 9 a.m.; diphenylhydantoin intoxication (?); nystagmus
2/28 12 m.	Pronounced	IV	Psychomotor seizure at 11:30 a.m.
3/3	Mild	I	No further seizures
4/9	None	Normal pattern	No further seizures; patient receiving phenobarbital therapy

CASE 10.—*J. S., a man aged 21. Chronic ulcerative colitis. Duration of delirium before first examination unknown. Admission, September 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/6	Mild	I	Bloody diarrhea; fever; loss of weight for two to three months
10/15	None	Normal pattern	Decrease in fever, diarrhea and evidence of toxicity

CASE 11.—*J. L., a man aged 49. Hypertensive heart disease; chronic alcoholism; nutritional deficiency; congestive heart failure. Duration of delirium before first examination, more than two weeks. Admission, March 6, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/16	Mild	II-I	Increasing delirium with sense deceptions, but notable improvement in preceding 4 days; venous pressure 120 mm. of water; circulation time 18 sec.
3/26	None	Normal fast pattern*	Compensated heart disease

* The last electroencephalogram showed predominantly fast, 13 to 19 per second activity, with an amplitude of 5 to 20 microvolts. We considered this the patient's normal pattern.

CASE 12.—*J. T., a man aged 74. Arteriosclerotic heart disease; congestive heart failure. Duration of delirium before first examination unknown. Admission, Sept. 20, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
9/26	Mild	I	Minimal evidences of congestive heart failure; circulation time 22 sec.; confusion greatly decreased by this time
9/30	None	I to normal pattern	No evidence of congestive heart failure

From the protocals it may be seen that at the time of initial study 4 patients showed stage IV electroencephalograms, 2 patients stage V electroencephalograms, 4 patients stage II electroencephalograms and 2 patients stage I electroencephalograms. The diagnoses are indicated in italics. The 6 patients with stage IV or stage V electroencephalograms were all greatly confused at the time of initial examination. The more irregular and disorganized slow activity (stage IV) was associated with delirium of more acute onset (of two weeks' duration or less), while the 2 patients with the regular but very slow rhythm had been delirious for three to five weeks or longer. The electroencephalograms of all the patients, however, showed complete, or almost complete, reversibility to a normal pattern. The remaining 6 patients with stage I or stage II electroencephalograms showed only mild to moderate disturbances in the level of awareness. At least 2 patients (J. L., case 11, with chronic alcoholism and congestive heart failure, and H. O., case 7, with typhus) were recovering at the time of the first examination, and probably the electroencephalograms would have manifested more conspicuous changes if they had been taken earlier.

E. M. (case 9), with epilepsy, offered an unusual opportunity for observation of the electroencephalogram and the mental status preceding and immediately after two typical psychomotor seizures. Two minutes after the second seizure, during which the patient sat up, stared, turned to the right and showed rhythmic chewing motions, she was greatly confused, and the electroencephalogram showed a dominantly slow (3 to 7 per second) and moderately irregular record, with many high voltage 3 per second waves. This record was indistinguishable from that for other patients with severe delirium except that the individual waves were somewhat more regular and more nearly sinusoidal. When the patient was examined again, after a six week period of freedom from seizures, the electroencephalogram was entirely normal, showing 84 per cent 8 to 10 per second activity, 15 per cent low voltage fast activity and only 1 per cent 7 per second activity (fig. 2).

One other patient (H. C., case 2, a boy aged 13 years, with acute glomerulonephritis) probably also had epilepsy. The onset of his delirium was accompanied by convulsions, and the electroencephalograms taken during recovery, while showing 75 per cent normal frequencies, still revealed paroxysmal groups of slower (6 to 7 per second) waves appearing spontaneously and a wave and spike pattern on hyperventilation. Again, the records taken during maximal confusion were undistinguishable from those of other extremely delirious patients (fig. 3).

The following case is illustrative of group I.

CASE 1.— M. R., a saleswoman aged 28, with a history of chronic addiction to alcohol for five years or more, noticed painful calves and burning of the feet three to four months before her admission to the hospital; this condition had been getting worse. One week before admission she embarked on a drinking spree and quickly became acutely intoxicated. She then showed increasing disturbance in awareness, tremor, overactivity and sensory deceptions, and three days later she lapsed into stupor. She was admitted to the Peter Bent Brigham Hospital in this state, on Jan. 1, 1942.

Examination.—The patient was somewhat obese. She was semistuporous and showed little spontaneous activity. She responded to painful stimuli by grimacing and mumbling and with aimless movements of the extremities. Movements of the eyes were limited and incoordinated. The pupils reacted to light. There was occasional rigidity on passive movements of the extremities. The tendon reflexes were overactive. The abdominal reflexes could not be elicited. The rest of the physical examination revealed nothing pertinent except evidences of dehydration.

Examination of the cerebrospinal fluid revealed normal pressure and dynamic state, no cells and a total protein content of 43 mg. per hundred cubic centimeters. Examination of the urine, blood and stools revealed nothing abnormal.

Course of Illness.—First Examination (Jan. 2, 1942): The patient was semistuporous and muttered incoherently. No formal status could be established. The results of neurologic examination were the same as those previously noted.

Second Examination (January 5): The patient had received intravenous injections of dextrose in isotonic solution of sodium chloride and then tube feedings, but no supplemental vitamins were given. She had begun to improve spontaneously on the second day of hospitalization. Ocular movements were now normal, and rigidity had disappeared.

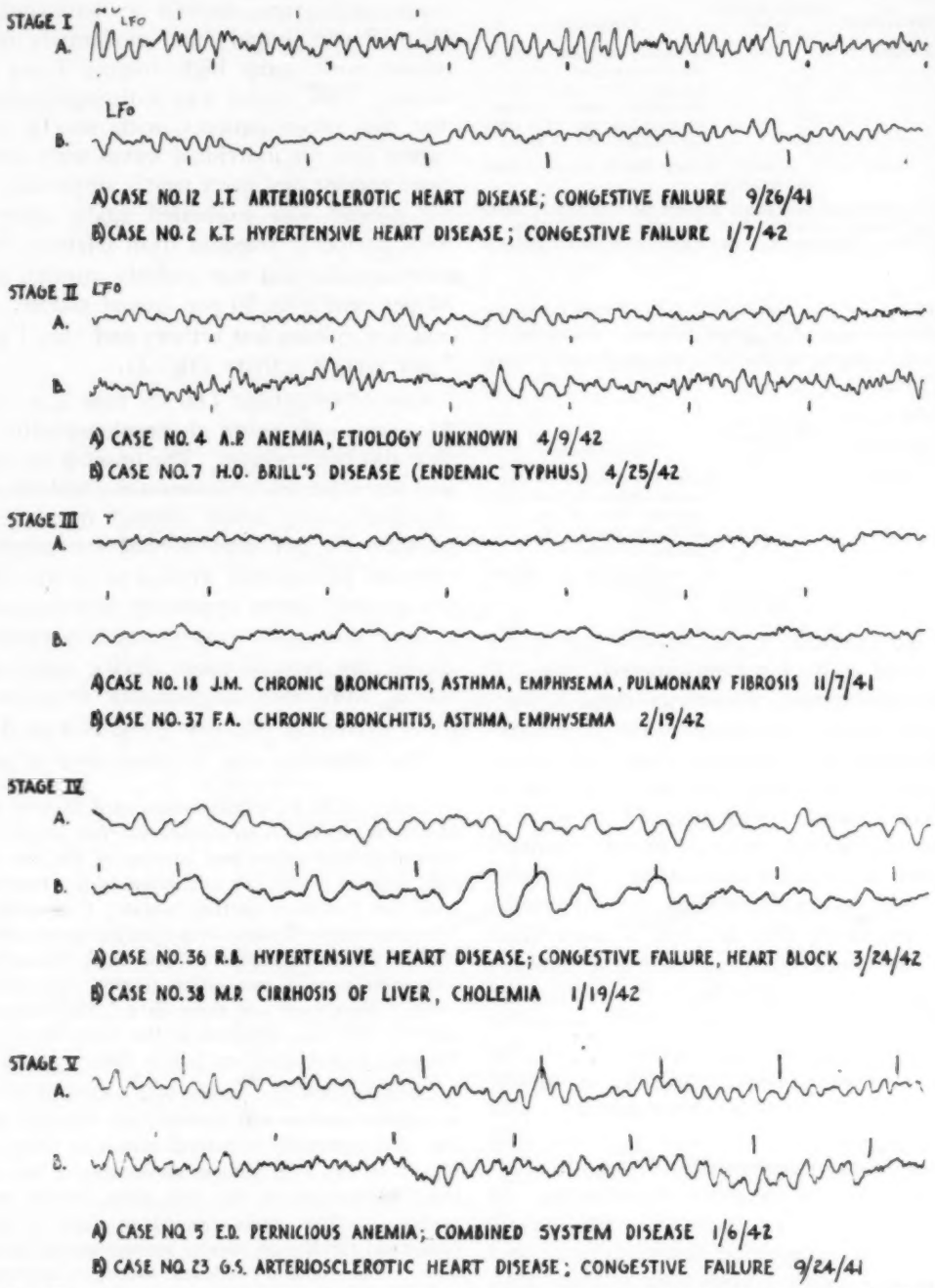

Fig. 1.—The five electroencephalographic stages (see text for description). Each stage is illustrated by samples from 2 cases.

The electroencephalogram was irregular throughout, with large, high voltage slow waves and superimposed, irregular, low voltage fast activity. There was no normal activity. This pattern represents stage IV (fig. 4).

The patient was no longer stuporous but was completely disoriented; she misidentified people, confabulated freely and showed marked fluctuation of attention.

Memory and ability to think abstractly were notably deficient. She rambled on from one topic to another through vague associations, as in a dream. She now presented the picture of a typical Korsakoff psychosis.

The electroencephalogram at this time showed chiefly irregular, low voltage fast activity, with persistence of some large, slow waves, and little, if any, normal activity. This record represented a transition to stage III.

nizable frequencies (24 per cent) in the normal range, which, however, were poorly organized. This record represented stage III.

Fourth Examination (January 12): The patient was now much more alert and more correctly oriented. She stated that she felt as if she had just awakened from a long and disturbing dream. Attention was fair, and she was able to subtract serially, with some errors.

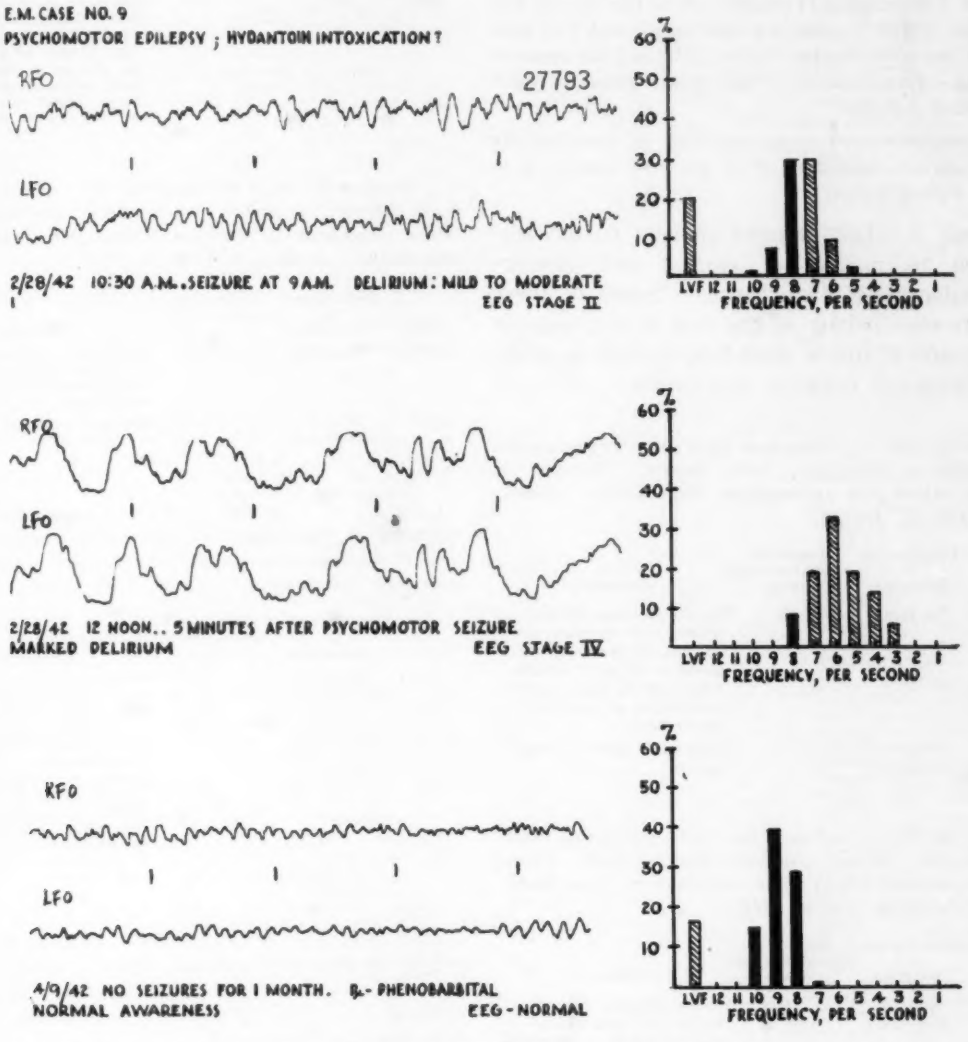

Fig. 2.—Electroencephalograms immediately before and after a psychomotor seizure.

The first electroencephalogram represented stage II and was taken during mild to moderate delirium one and a half hours after a typical psychomotor seizure and one and one-half hours before a second seizure. Five minutes after the second seizure confusion was severe and the electroencephalogram was of stage IV type. Six weeks later, after no seizures for one month and with adequate therapy, the electroencephalogram was normal, and there was no disturbance in awareness.

Third Examination (January 7): The patient was still disoriented and confabulated freely. Attention and memory were defective. She read with many errors and was unable to comprehend or relate what she had read. She still recounted dreamlike experiences as though they were real.

The electroencephalogram was still irregular, with much low voltage fast activity, but with more recognizable frequencies (24 per cent) in the normal range, which, however, were poorly organized. This record represented stage III.

Reading and memory for stories were much better, although she still confabulated moderately in filling in details. Interpretation of proverbs was fairly good.

The electroencephalogram showed beginning organization and regularity, with 49 per cent normal frequencies, mixed with some low voltage fast (33 per cent) activity and slow (5 to 7 per second) activity (19 per cent). This record represented stage II.

Fifth Examination (January 16): The patient was now correctly oriented; attention was sustained; memory was intact in all categories; ability for abstract thinking was good, and she no longer confabulated. The spontaneous content of thought seemed normal.

The electroencephalogram was now regular, with 61 per cent normal activity, 8 per cent 6 to 7 per second activity and 31 per cent low voltage fast activity. This record represented stage I.

Sixth Examination (February 15): The patient had been out of the hospital for one month and had been back at her work for two weeks. She had not resumed drinking. Examination of the mental status revealed no residual defects.

The electroencephalogram was now an unequivocally normal record, consisting of 89 per cent regular, 8 to 12 per second activity.

Group 2.—Ten patients showed partial restoration to normal of clinical and electroencephalographic disturbances. Some of these patients may belong to the first group, but we were unable to follow them long enough to establish evidence of complete restoration.

CASE 13.—*A. C., a woman aged 55. Hypertensive heart disease; congestive heart failure. Duration of delirium before first examination, three weeks. Admission, April 25, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/27	Severe	IV	Venous pressure 150 mm. of water, with increase to 200 mm. of water on compression of liver; circulation time 26 sec.; oxygen saturation of arterial blood 80%
5/7	Severe to moderate	III-IV	Diminished signs of heart failure

CASE 14.—*L. S., a man aged 60. Arteriosclerotic heart disease; chronic congestive heart failure. Duration of delirium before first examination, four weeks plus. Admission, Jan. 9, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/20	Mild to moderate	III (fig. 5)	Venous pressure 180 mm. of water, with rise to 230 mm. of water on compression of liver; circulation time 53 sec.; oxygen saturation of arterial blood 90%
1/24	Severe	IV	Degree of congestive failure unchanged; venous pressure 180 mm. of water, with rise to 250 mm. of water on compression of liver; circulation time, no end point
1/26	Moderate	IV	Venous pressure 140 mm. of water, with rise to 180 mm. of water on compression of liver; circulation time 49 sec.
2/12	Mild	II-I	No clinical evidence of congestive heart failure; patient ready to be discharged

CASE 15.—*W. F., a woman aged 54. Acute coronary occlusion; congestive heart failure. Duration of delirium before first examination, three to four weeks. Admission, Sept. 16, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/2	Severe	III-IV	Venous pressure 180 mm. of water; circulation time 43 sec.; Cheyne-Stokes respiration
10/23	Mild	II-I	Degree of congestive failure much diminished; normal respiration; venous pressure 40 mm. of water, with no rise on compression of liver; circulation time 33 sec.; oxygen saturation of arterial blood 95.8%

CASE 16.—*M. D., a woman aged 65. Arteriosclerotic heart disease; congestive heart failure; auricular fibrillation. Duration of delirium before first examination, two weeks. Admission, Oct. 10, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/21	Moderate	II-III	Enlarged heart; bilateral hydrothorax; basal rales; improvement in patient's condition
10/27	Mild to moderate	I	Minimal evidence of heart failure

CASE 17.—*J. S., a man aged 45. Chronic alcoholism; malnutrition; malignant retroperitoneal tumor. Duration of delirium (intermittent) before first examination, one year. Admission, Jan. 27, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/27	Moderate to severe	V	Patient had been much more delirious but was responding to transfusions, high caloric diet and administration of supplemental vitamins
5/8	Moderate	I	Patient had greatly improved in home for convalescents; April 20 abdominal pain developed; laparotomy (5/4) revealed a malignant retroperitoneal tumor

CASE 18.—*J. M., a man aged 49. Chronic bronchitis, asthma, emphysema, pulmonary fibrosis; failure of right side of heart; secondary polycythemia.* Duration of delirium before first examination, one month. Admission, Nov. 3, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/6	Moderate	III	Intense cyanosis; oxygen saturation of arterial blood 56%; carbon dioxide content 59.8 volumes %
11/7	No tests	III	Oxygen saturation of arterial blood 50%; carbon dioxide content 56.4 volumes %
11/10	Mild	III-II	Oxygen saturation of arterial blood 71.4%; carbon dioxide content 58.2 volumes %
11/13	Mild	II	Oxygen saturation of arterial blood 84.3%; carbon dioxide content 53.9 volumes %

* The patient died at home some months later. Autopsy was not performed.

CASE 19.—*G. A., a man aged 60. Chronic bronchitis and asthma; emphysema; failure of right side of heart; polycythemia. Duration of delirium before first examination, two to three weeks. Admission, Dec. 1, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/3	Moderate	III	Oxygen saturation of arterial blood 79%; carbon dioxide content 59.2 volumes %; red blood cells 6,290,000 per cu. mm.; venous pressure 210 mm. of water; circulation time 20 sec.; vital capacity 1,500 cc.
12/16	Mild	III-II	Oxygen saturation of arterial blood 87.3%; carbon dioxide content 54.05 volumes %; venous pressure 75 mm. of water; circulation time 19 sec.; vital capacity 1,800 cc.
12/19	Mild	II-I	Oxygen saturation of arterial blood 88.5%; carbon dioxide content 55.5 volumes %

CASE 20.—*D. Mc., a girl aged 13 years. Chorea minor; acute rheumatic heart disease; congestive heart failure. Duration of delirium before first examination, six days. Admission, Jan. 10, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/12	Severe	IV	Severe chorea; mutism; temperature 103 F.; moderate left ventricular failure
1/22	Moderate	IV-III	Temperature normal for 3 days; decreased pulmonary congestion
2/14	Mild	II-I	Patient afebrile and free from chorea for 2 weeks
2/19	Mild	II-I	No change in patient's condition

CASE 21.—*E. M., a woman aged 62. Addison's disease; pulmonary tuberculosis. Duration of delirium before first examination, six weeks. Admission, March 18, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/20	Moderate	II	Urea nitrogen 21 mg. per 100 cc.; sodium 120 mEq./L.; chloride 89 mEq./L.; blood pressure 105/70; weight 45.6 Kg.; hematocrit reading 48%
3/27	Mild	Normal	3/20-3/27: 20 mg. of desoxycorticosterone acetate and 95 cc. of adrenal cortex extract (Upjohn) injected intramuscularly (20 cc. of extract 3/27); 15 Gm. of sodium chloride daily; sodium 134 mEq./L.; chloride 104 mEq./L.; temperature 101 F.
4/7	Mild to moderate	I-II	3/28-4/7: 2 mg. of desoxycorticosterone acetate injected intramuscularly daily; 5-11 Gm. of sodium chloride daily weight 50 Kg.; blood pressure 124/70 to 170/100; hematocrit reading 28%; sodium 140 mEq./L.; chlorides 111 mEq./L.; temperature 99 to 101 F.; roentgenogram of the chest showed increase of exudative lesions
4/13	Mild	I	4/8-4/11: 10 cc. adrenal cortex extract daily; 4/12: 20 cc. of extract; 4/13: 38 cc. of extract and 9 Gm. sodium chloride daily; weight 47.8 Kg.; blood pressure 140/90 to 150/110; hematocrit reading 28%

CASE 22.—*R. W., a man aged 59. Addison's disease. Duration of delirium before first examination unknown. First admission, Oct. 6, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/10/41	Mild	II	Mild crisis. Blood pressure 102/70; sodium 130 mEq./L.; hematocrit reading 47%; no medication; weight 76.8 Kg.
10/15	Mild	II	Crisis more severe. Blood pressure 85/50; sodium 130 mEq./L.; 1 injection of 10 mg. desoxycorticosterone acetate and 1 injection of 5 cc. adrenal cortex extract; 60 Gm. sodium chloride in 3 days
10/22	Mild	II	Medication: 3 mg. desoxycorticosterone acetate daily; 9 Gm. of sodium chloride daily. Hematocrit reading 46%; sodium 135 mEq./L.
11/7	Mild	II-I	Medication: 1 mg. desoxycorticosterone acetate daily; 4 Gm. of sodium chloride daily. Hematocrit reading 39%; sodium 140 mEq./L.; blood pressure 125/90; weight 74.6 Kg.
11/12	None	I	Medication same as that for 11/7. Hematocrit reading 40%; blood pressure 125/73. Patient discharged from hospital
12/15	None	I	Good clinical condition: blood pressure 100/85. Medication: 1 mg. desoxycorticosterone acetate daily; 5 Gm. sodium chloride daily; 60 mg. thiamine hydrochloride daily *
1/3/42	None	I	Clinical condition good. Medication: 1 mg. desoxycorticosterone acetate daily; 6 Gm. of sodium chloride daily; 300 mg. nicotinamide daily. Blood pressure 120/80
2/20	None	I	Clinical condition good. Medication: desoxycorticosterone acetate and sodium chloride same as that of 1/3; 25 mg. calcium pantothenate daily. Weight 81.2 Kg.; blood pressure 125/75; hematocrit reading 44%
3/31	None	I	Clinical condition good. Medication: desoxycorticosterone acetate and sodium chloride same as before; 12 mg. riboflavin daily. Weight 82 Kg.; sodium 137 mEq./L.; chloride 110 mEq./L.
4/4	None	I to normal pattern	Clinical condition good. Medication: 15 cc. adrenal cortex extract daily for 4 days; 47.5 cc. of extract on 4/4
4/14	Mild	II	Mild crisis; acute pyelitis; temperature 102 F. Medication (4/8 to 4/14): desoxycorticosterone acetate 3 to 7 mg. daily; adrenal cortex extract 10 to 20 cc. daily; dextrose in saline solution, 4 to 6,000 cc.; 1 Gm. sulfadiazine daily. Hematocrit reading 47 to 36%; sodium 127 mEq./L.; blood pressure 110/70 to 125/80

* Merck & Company, Inc., Rahway, N. J., furnished the vitamins used in this experiment.

Of this group of 10 patients, the electroencephalograms of 5 showed evidence of stage IV or stage V. This most prominent electroencephalographic abnormality correlated in each

instance with severe disturbances of awareness. Although the period of delirium was difficult to determine accurately, the estimated duration previous to the first examination ranged from six days to three to six weeks, except in the case of J. S. (case 17), who had been known to be confused intermittently for perhaps one year. This patient had a stage V electroencephalogram. The clinical condition of L. S. (case 14) became worse between his first and his second examination, this change being reflected in the electroencephalogram (fig. 5). Three patients showed degree of change in the electroencephalogram disparate with his psychologic status. One of the most interesting evidences of the primary disturbance in carbohydrate metabolism in this patient was the hypoglycemic reactions, with confusion and increasingly abnormal electroencephalographic changes, which occurred at levels of the blood sugar not usually associated in normal persons with such pronounced clinical signs and symptoms of hypoglycemia. This phenomenon, which has been pointed out previously,[10] suggests the possibility of a lowered threshold of

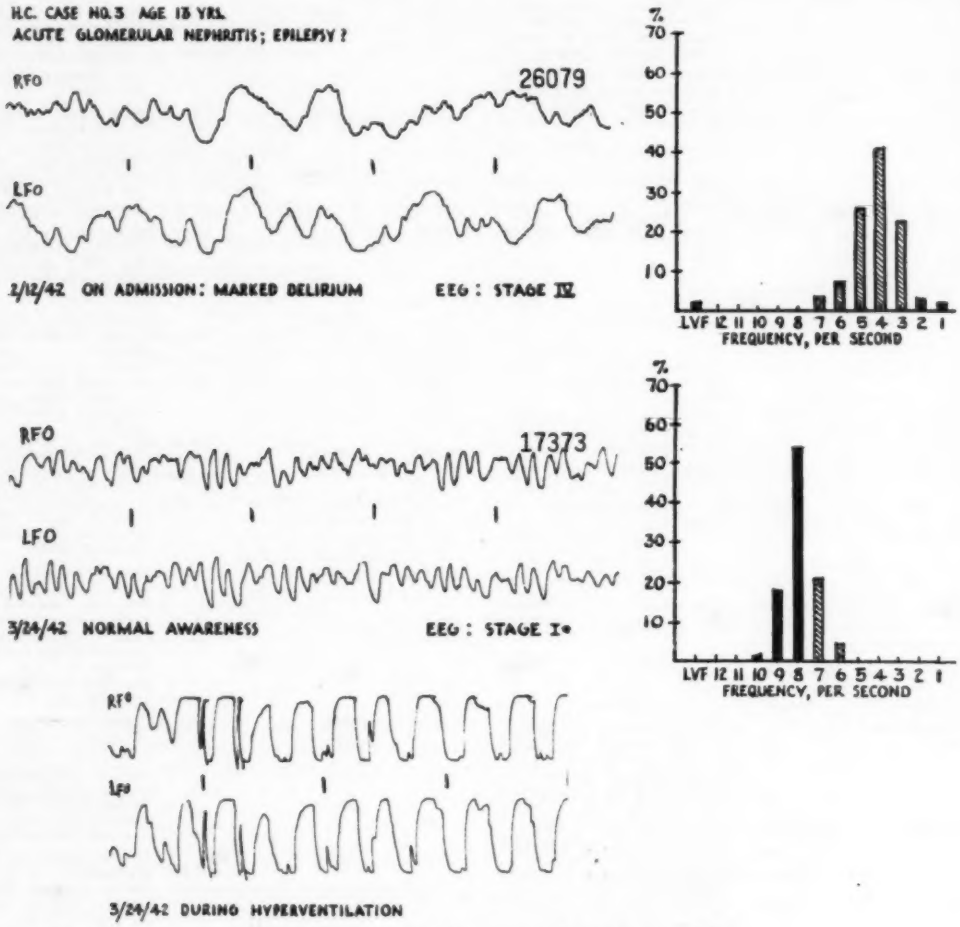

Fig. 3.—Delirium in a case of probable epilepsy with acute glomerulonephritis.

After the delirium had completely cleared, the electroencephalogram still showed runs of high voltage slow waves among normal frequencies, and on hyperventilation a wave and spike pattern appeared.

stage II electroencephalograms and were considered to be moderately confused. The remaining 2 patients with stage II electroencephalograms had Addison's disease. The electroencephalograms of patients with Addison's disease have been shown to be abnormal[6] even when replacement therapy is presumably adequate and the patient has returned to normal social activity. One of the 2 patients with this disease (R. W., case 22) presented a reaction in patients with Addison's disease. Both patients with this condition were in mild crisis at

10. Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Investigation **19**:813, 1940. Engel, G. L., and Margolin, S. G.: Neuropsychiatric Disturbances in Addison's Disease and the Role of Impaired Carbohydrate Metabolism in the Production of Abnormal Cerebral Function, Arch. Neurol. & Psychiat. **45**:881 (May) 1941.

the time of initial examination and showed mild to moderate confusion. R. W. responded well clinically to desoxycorticosterone acetate; although the electroencephalographic pattern improved, it remained abnormal when no evidences of disturbed awareness could be elicited. Repeated examinations over the course of five months of treatment with desoxycorticosterone acetate and various supplemental vitamins of the B complex group revealed no essential change.

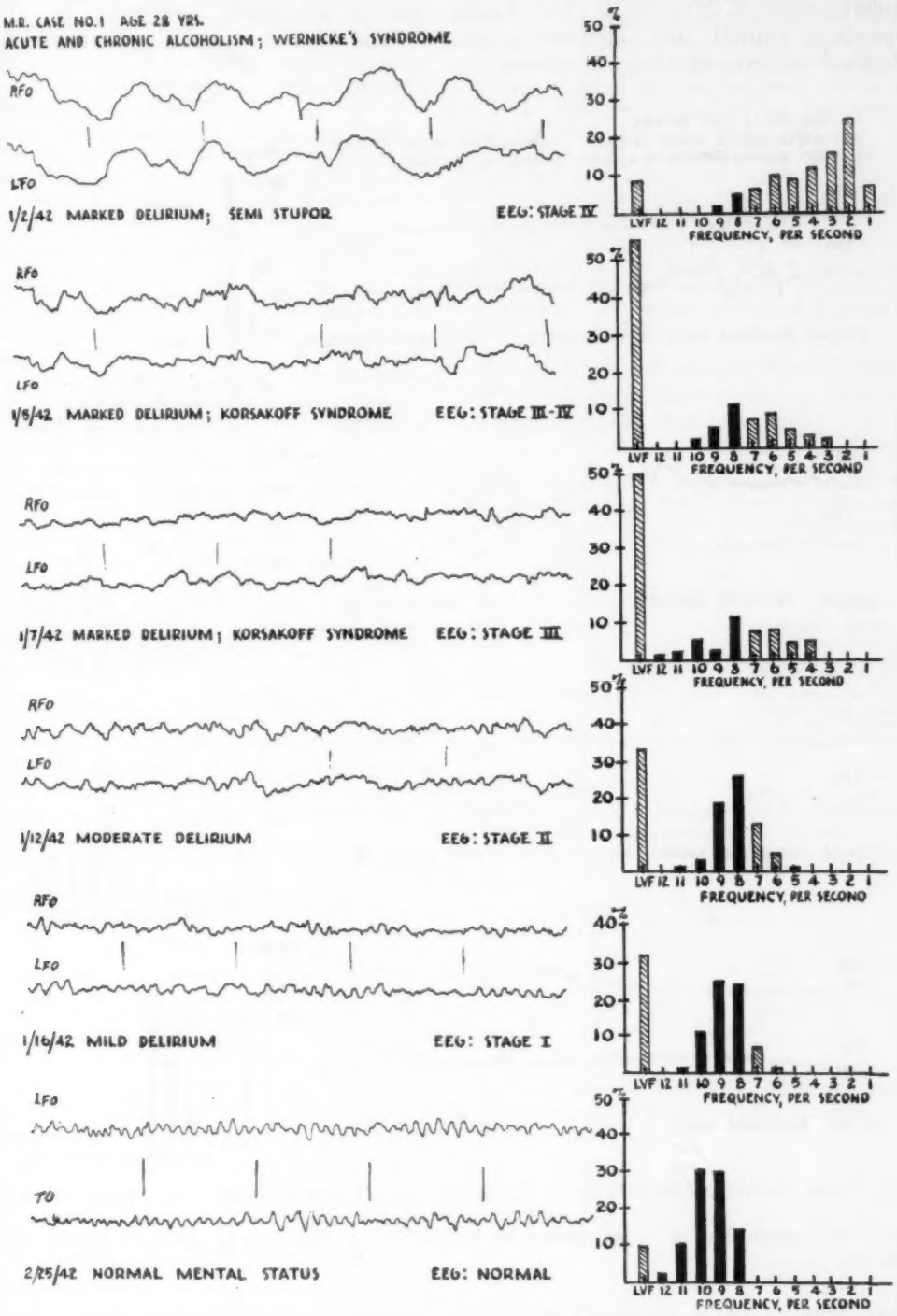

Fig. 4.—Complete recovery in a case of acute and chronic alcoholism with Wernicke's encephalopathy. The electroencephalogram passed through all phases from stage IV to normal, with corresponding improvement in the mental status.

After administration of 107 cc. of adrenal cortex extract (Upjohn) [11] in five days, the electroencephalogram became nearly normal, and no hypoglycemic reaction developed during the dextrose tolerance test. E. M. (case 21) also showed corresponding clinical and electroencephalographic improvement with 95 cc. of adrenal cortex extract, administered in six days. The electroencephalogram in this case became entirely normal. The presence of infection (E. M., case 21, with exacerbation of pulmonary tuberculosis, and R. W., case 22, with acute pyelitis) prevented repetition of these experiments.

A more detailed report on the electroencephalogram and the cerebral metabolism in Addison's disease will appear later.[12]

The following case is illustrative of group 2 (fig. 5):

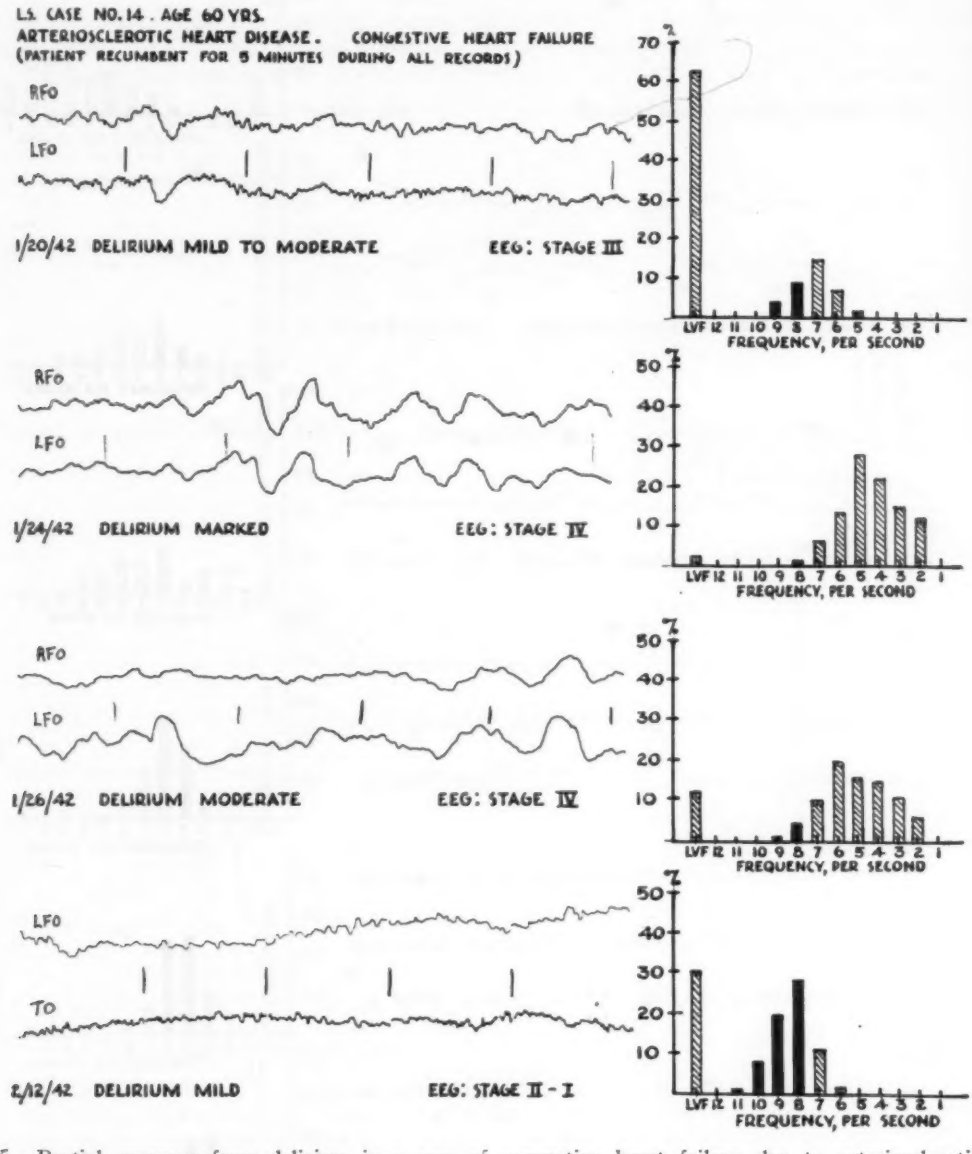

Fig. 5.—Partial recovery from delirium in a case of congestive heart failure due to arteriosclerotic heart disease.

Clinically the patient became worse before he became better, and this is also apparent in the electroencephalogram.

History.—L. S. (case 14), a Negro aged 66, was admitted to the Peter Bent Brigham Hospital on Jan. 19, 1942 because of increasing dyspnea.

11. The Upjohn Company, Kalamazoo, Mich., supplied the adrenal cortex extract.

12. Romano, J., and Engel, G. L.: The Significance of the Electroencephalographic Changes in Addison's Disease, to be published.

The patient had first manifested exertional dyspnea and paroxysmal nocturnal dyspnea two years before. On admission to the hospital at that time he had peripheral edema, pulmonary congestion, an enlarged heart and hypertension (155 systolic and 115 diastolic), and the electrocardiogram showed a prolonged PR interval and intraventricular block. He improved rapidly under a regimen of rest and administration of digitalis and diuretics. After discharge he was observed in the outpatient department.

Five weeks before admission increasing dyspnea, attacks of paroxysmal nocturnal dyspnea, edema of the ankles and swelling of the abdomen developed, and he gained 14 pounds (6.4 Kg.) in weight in two and a half weeks.

Examination.—Physical examination revealed dyspnea and orthopnea. The veins of the neck were distended and filled further on compression of the liver. The heart was enlarged to the left anterior axillary line, where a prominent apical impulse was noted in the sixth interspace. The blood pressure was 105 systolic and 85 diastolic. There were dulness and diminished breath sounds at the base of the right lung, and moist rales were heard in both lungs up to the angle of the scapula. There was ascites, and the edge of the liver was felt 3 fingerbreadths below the costal margin. There was pronounced pitting edema over the sacrum and legs.

Course of Illness.—First Examination (January 20): The patient was jocular and somewhat euphoric. He was correctly oriented. Memory and recall were defective. Attention was fair, and he carried out serial subtraction tests methodically, but with several errors. He interpreted proverbs well. There was no confabulation, either spontaneous or provoked.

Electroencephalogram (fig. 5): With the patient lying almost flat, the test was begun immediately; the record was predominantly one of low voltage fast activity, with 24 per cent 5 to 7 per second activity and 13 per cent 8 to 9 per second activity (stage III).

Physiologic data are listed in the accompanying tabulation (case 14).

Second Examination (January 24): There had been moderate diuresis, with decrease in edema, but the patient was still dyspneic and othopneic and experienced frequent episodes of paroxysmal nocturnal dyspnea. He was now noted to be confused at night, mistook his room for "a small room in the First National Bank," "a movie theater" or "Massachusetts Avenue" and experienced disturbing dreams. Examination revealed little change in the degree of congestive heart failure. When the patient was tested in the laboratory, he appeared confused and bewildered. He expressed the feeling that he was now living in "Biblical times" and that each minute represented "a thousand years." He spoke about the Bible and religion, intermingling these comments with more prosaic conversation. He was somewhat irritable. Attention fluctuated considerably, and he was unable to carry out serial subtractions. Memory was poor, and he had difficulty in interpreting proverbs.

The electroencephalogram was irregular and slow, with many large slow waves (stage IV).

Third Examination (January 26): Signs of congestive heart failure had diminished somewhat. The patient was more quiet and less irritable. He was still confused and referred frequently to religious matters. He was correctly oriented, but attention fluctuated and memory was only fair. He was now able to do serial subtractions, but with numerous errors and frequent loss of place. He had difficulty in interpreting proverbs, and confabulation could be provoked.

Electroencephalogram: At the onset of the examination and with the patient recumbent, the electroencephalogram showed predominantly slow activity, which was somewhat less irregular than on the previous occasion. The pattern was still that of stage IV.

Fourth Examination (February 12): The patient had now largely recovered from the heart failure and was ready for discharge. He had not been confused at night for more than ten days. He was correctly oriented and more attentive. Memory was still defective, and serial subtraction was done with a number of errors, although with better sustained attention. Some confabulation could still be provoked.

The electroencephalogram now showed a beginning regular pattern, with 58 per cent normal frequencies, 13 per cent 6 to 7 per second activity and 31 per cent fast activity. The record represented a phase between stage II and stage I.

Group 3.—Eight patients showed little or no change in the level of awareness or became worse during the period of observation.

CASE 23.—*G. S., a woman aged 71. Hypertension and arteriosclerotic heart disease; congestive heart failure. Duration of delirium before first examination, one year. Admission, Sept. 22, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
9/24	Severe	V	Moderately severe congestive heart failure
9/26	Severe	V	Less severe congestive heart failure
10/9	Severe	V	No congestive failure; slight shift toward faster and more normal frequencies in electroencephalogram

CASE 24.—*S. F., a woman aged 54. Rheumatic valvular disease; chronic congestive heart failure. Duration of delirium before first examination, one year. Admission, Sept. 26, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
9/29	Severe	V	Severe congestive heart failure
1/6	Severe	V	Severe congestive heart failure

CASE 25.—*O. K., a woman aged 23. Libman-Sacks syndrome with dermatomyositis; severe emaciation.* Duration of delirium before first examination unknown. Admission, Feb. 12, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/14	Moderate	IV-V	Five year history of intermittent involvement of joints, skin, lungs and muscles, with extreme emaciation; onset of present episode 3 months before admission. Weight 32.7 Kg.; temperature 102 F.
3/26	Moderate to severe	V	Weight 25.4 Kg.; extreme exhaustion and asthenia
4/23	Moderate	V	Some clinical improvement; weight 30 Kg.; temperature 101 F.

* The patient was discharged on May 1, 1942 to return home; she lapsed into coma and died May 3. An autopsy was performed.

CASE 26.—*W. F., a man aged 46. Malignant hypertension; uremia.* Duration of delirium before first examination, two to three weeks. Admission, Jan. 15, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/19	Severe	IV (fig. 6)	Blood pressure 240/165; cerebrospinal fluid pressure 410 mm. of water; nonprotein nitrogen 73 mg. per 100 cc.; venous pressure elevated; pulmonary congestion; Cheyne-Stokes respiration; hemoglobin 11.7 Gm. per 100 cc.
2/16	Mild	V	Numerous convulsive seizures and great confusion in first 3 wk. 2/6/42; considerable improvement; blood pressure 250/120; increase in urea nitrogen content of blood from 80 to 119 and 160 mg. per 100 cc.; carbon dioxide content 48 volumes %; chlorides 98 mEq./L.; hemoglobin 8 Gm. per 100 cc.

* The patient died in the hospital in the latter part of February 1942. Autopsy was performed.

CASE 27.—*J. M., a man aged 74. Chronic alcoholism; cirrhosis of liver; pneumonia; acute empyema; congestive heart failure. Duration of delirium before first examination unknown. Admission, Dec. 11, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/24/41	Severe	IV	Icteric index 54; venous pressure 205 mm. of water; hemoglobin 10.9 Gm./100 cc. Pneumonic process subsiding; early evidence of empyema. Temperature 101 F.; oxygen saturation of arterial blood 94.2%
12/30	Less severe	IV-V	Icteric index 40; temperature 99-100 F.
1/16/42	Unchanged	IV-V	Icteric index 18; temperature 100.5 F.; venous pressure 100 mm. of water, with increase on compression of liver to 200 mm. of water; oxygen saturation of arterial blood 94.7%
1/21	Unchanged	V	Empyema
4/30	Unchanged	V	Area of empyema drained surgically 1/26/42. Clinical improvement; no icterus or congestive heart failure. Wound well healed. Patient followed in outpatient department

CASE 28.—*S. J., a man aged 60. Tuberculous pericarditis; exfoliating erythrodermatitis; emaciation.* Duration of delirium before first examination, two weeks (?). Admission, Dec. 8, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/18	Mild	I	Hydrothorax and ascites; venous pressure 55 mm. of water; circulation time 15 sec.; vital capacity 1,300 cc.; fever
1/9	Not tested	II	Severe ulcerative stomatitis, exfoliative dermatitis and generalized edema. Patient appeared drowsy but could not be tested formally because of oral lesions

* The patient died in the hospital on Jan. 18, 1942. Autopsy was performed.

CASE 29.—*S. H., a man aged 63. Addison's disease.* Duration of delirium before first examination, six weeks (?). Admission, Feb. 9, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/13	Moderate	III (?)	Mild crisis. Blood pressure 92/68; hematocrit reading 41%; urea nitrogen content of blood 30 mg./100 cc.; sodium 136 mEq./L.; chlorides 102 mEq./L. Medication: 6 Gm. sodium chloride daily. Weight 43 Kg.
3/9	Moderate; slight improvement	III to II (?)	Blood pressure 100/60; weight 47.2 Kg.; sodium 131 mEq./L.; hematocrit reading 35%. Medication: 15 Gm. sodium chloride daily; 4 cc. of adrenal cortex extract (of doubtful potency) daily for 4 days
5/8	Unchanged	III to II (?)	Patient discharged from hospital 3/9. Since 4/7 daily administration of 1 mg. desoxycorticosterone acetate and 15 Gm. sodium chloride. 4/13: sodium 119 mEq./L. 5/8: poor appetite, weakness and fatigue; blood pressure 105/75; sodium 147 mEq./L.; chlorides 112 mEq./L.

* The therapy of this patient was not under our direct supervision.

CASE 30.—*A. S., a woman aged 59. Pernicious anemia; combined system disease. Duration of delirium before first examination, six weeks (?). Admission, Feb. 26, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/6	Moderate	III (?)	Hemoglobin 7.6 Gm./100 cc.; red cells 2,000,000 per cu. mm.; reticulocyte count 18%. Since 2/27 daily intramuscular injections of 1 cc. liver extract
3/24	Moderate	III (?)	Hemoglobin 9.7 Gm./100 cc.; red cells 3,110,000 per cu. mm.
5/9	Slight improvement	III (?)	Liver therapy stated to be adequate; patient followed in outpatient department

The 8 patients in this group were all chronically ill. For a number it was not possible to establish the total duration of the delirium, but several apparently had had disturbances in awareness for as long as a year. The factors responsible for the prolongation of the delirious state varied. Three patients (cases 23, 27 and 30) undoubtedly had long-standing vascular and degenerative changes associated with age which greatly decreased the essential reversibility of the reaction to the underlying physical disease. The other patients suffered from diseases which ran a chronic, and often progressive, course. The patient with Addison's disease had not received adequate replacement therapy on any of the three occasions on which she was studied.

Three patients (cases 25, 26 and 28) in this group eventually died. Two of these patients (cases 25 and 28) presented postmortem evidence of cerebral edema. In the other patient (case 26), with dermatomyositis, numerous infil-

trative lesions of small vessels leading to small, granuloma-like foci of gliosis were noted in the brain. The question of morphologic alterations in the brain will be discussed in a subsequent section.

Correlation of the electroencephalogram with the mental status was again good. Five patients were greatly confused, and all had stage IV to stage V electroencephalograms. The 2 patients with stage III electroencephalograms showed moderate confusion, while S. J. (case 28), with a stage I electroencephalogram, was only mildly confused. There was some uncertainty in the interpretation of the electroencephalograms of A. S. (case 30) and S. H. (case 29). Both these records consisted chiefly of irregular, low voltage fast activity with small amounts of irregular, slow activity. Both the patients showed moderate disturbances in the level of awareness, but as neither the clinical state nor the electroencephalogram changed significantly during the period of observation, we cannot state with finality that this electroencephalographic pattern represented stage III, and not a normal low alpha record. We hope to be able to settle this point by observing other patients with records of this type who improve clinically.

W. F. (case 28) demonstrated the transition of the electroencephalographic pattern from stage IV to stage V (fig. 6). This patient, a man aged 46, entered the hospital with malignant hypertension and hypertensive encephalopathy. At the time of admission the blood pressure was 240 systolic and 165 diastolic; there was evidence of left and right ventricular failure, and the cerebrospinal fluid pressure was elevated to 410 mm. of water. The nonprotein nitrogen content of the blood was 73 mg. per hundred cubic centimeters. The patient was extremely confused; his attention fluctuated greatly during Cheyne-Stokes respiration, and the electroencephalogram was totally disorganized, irregular and slow. He remained in this state for three weeks, during which period a number of convulsions occurred. When the patient was reexamined about one month later, the degree of confusion had lessened considerably; convulsions had ceased, but there were increasing retention of urea nitrogen and anemia. The electroencephalogram at this stage showed a great increase in regularity but was still predominantly slow, and there was no change when the patient opened his eyes. Several days after this the patient lapsed into coma and died.

These changes are illustrated in figure 6.

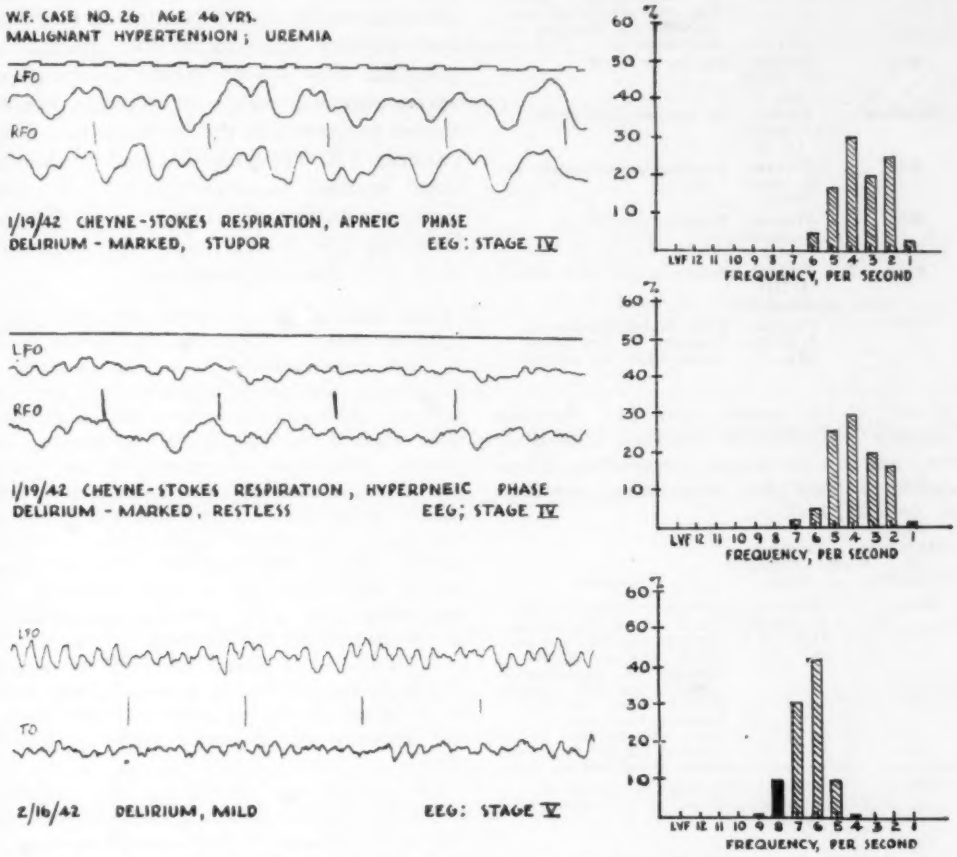

Fig. 6.—Progression from stage IV to stage V in a case of prolonged delirium due to malignant hypertension and uremia. A phasic difference during Cheyne-Stokes respiration is also illustrated. In this patient the mental status improved considerably during the transition from stage IV to V.

Group 4.—Three patients presented electroencephalographic changes indicative of focal and diffuse cerebral involvement.

CASE 31.—*H. B., a man aged 55. Presenile cerebral atrophy; epilepsy. Duration of delirium before first examination unknown. Admission, Nov. 18, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/21/41	Mild	Frontal, III-IV; occipital, I	Recurrent spells of confusion and convulsions for preceding 5 yr. Clinical studies, including pneumoencephalographic tests, indicated presenile atrophy of frontal lobes. Patient had had generalized convulsion the morning of November 21
11/24	Mild	Frontal, IV, occipital, II	Seizure on 11/22
11/28	Moderate	Frontal, IV, occipital, II	No seizure since 11/22
12/4	Mild	Frontal, II, occipital, I	Pneumoencephalogram on 12/1
12/29	Mild	Frontal, II, occipital, I	Seizure on 12/28
1/9/42	None	Frontal, II-III; occipital, I-II	Seizure a few days before
3/30	None	Frontal, I; occipital, I	With diphenylhydantoin therapy, 0.1 Gm. three times daily; no seizures

CASE 32.—*R. G., a woman aged 54. Presenile cerebral atrophy (?); diabetes mellitus, controlled; hypertensive cardiovascular disease, compensated. Duration of delirium before first examination unknown. Admission, April 25, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/29	Severe	Frontal, IV; occipital, I-II	Diabetes controlled; questionable past history of cerebral vascular accident; blood pressure 190/110; pressure and dynamics of cerebrospinal fluid normal; protein 55 mg./100 cc.; lymphocytes 2 per cu. mm.; urea nitrogen of blood 13 mg./100 cc.; blood sugar 92 mg./100 cc.
5/8	Severe	Frontal, IV; occipital, I-II	No essential change in clinical or laboratory data

CASE 33.—*I. A., a woman aged 55. Meningitis (Pneumococcus type 17); thrombosis of leptomeningeal vessels; encephalomalacia.* Duration of delirium before first examination, one month. Admission, February 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/14/42	Severe	Left frontal region IV; occipital, II	Patient had received specific antipneumococcic serum and sulfadiazine; remained stuporous

* Patient died in the middle of March 1942. An autopsy was performed.

Each of the patients in this group had focal electrical disturbances which originated in the frontal areas and spread diffusely to a varying degree.

Although we used the previously noted classification of electroencephalographic stages for the records of this group, they presented certain noteworthy differences from those of the previous group. All these patients had foci in the frontal areas in which the electroencephalographic changes were comparable to the previously established gradations. Tracings taken simultaneously from the frontal, temporal, parietal and occipital areas revealed that the high potential slow waves originating in the frontal areas spread posteriorly, with a slight time lag and in a progressively diminishing proportion. The occipital region thus presented an essentially normal pattern interrupted by groups of high potential slow waves, which coincided with the appearance of waves of higher potential and slower frequency in the frontal area. Two of the patients (R. G., case 32, and I. A., case 33) were studied incompletely. I. A. died, and autopsy established evidence of encephalomalacia involving the frontal lobes. The further course of R. G.'s illness is unknown.

The case of H. B. (case 31) presented certain features worthy of comment. The patient, a man aged 55, had experienced spells of confusion for at least five years, and more recently had had convulsive seizures. Although his seizures had clonic phases, they were characterized principally by peculiar slow, repetitive, stereotyped movements of the face and the extremities. Confusion was evident at times before such seizures and usually occurred afterward. Occasionally the patient experienced peculiar aphasic-like confused periods without any disturbances in movement. His interim status was that of early dementia. Pneumoencephalographic study revealed considerable dilation of the ventricular and subarachnoid spaces. The left ventricle was more dilated anteriorly and was displaced slightly to the left, having apparently been drawn there by shrinkage of the left anterior frontal area. There was increased air about the island of Reil on both sides.

The patient was studied for five months, during which time he had occasional seizures and periods of confusion. Prominent electroencephalographic changes in the frontal areas were always noted during periods of confusion. However, on one occasion (January 9), two days after a seizure, there were moderate electroencephalographic changes in the frontal area although his awareness was good. After diphenylhydantoin therapy (one month), with no seizures, the electroencephalographic changes were minimal and his awareness was intact. These data, together with those obtained for H. C. (acute glomerulonephritis and epilepsy), group 1, case 3, lead us to believe that certain components of the electrical disturbances in epileptic patients are not directly correlated with changes in the level of awareness.

The electroencephalographic changes for H. B. are illustrated in figure 7.

Group 5.—This group of 11 patients consisted of persons who died before more than one examination could be carried out.

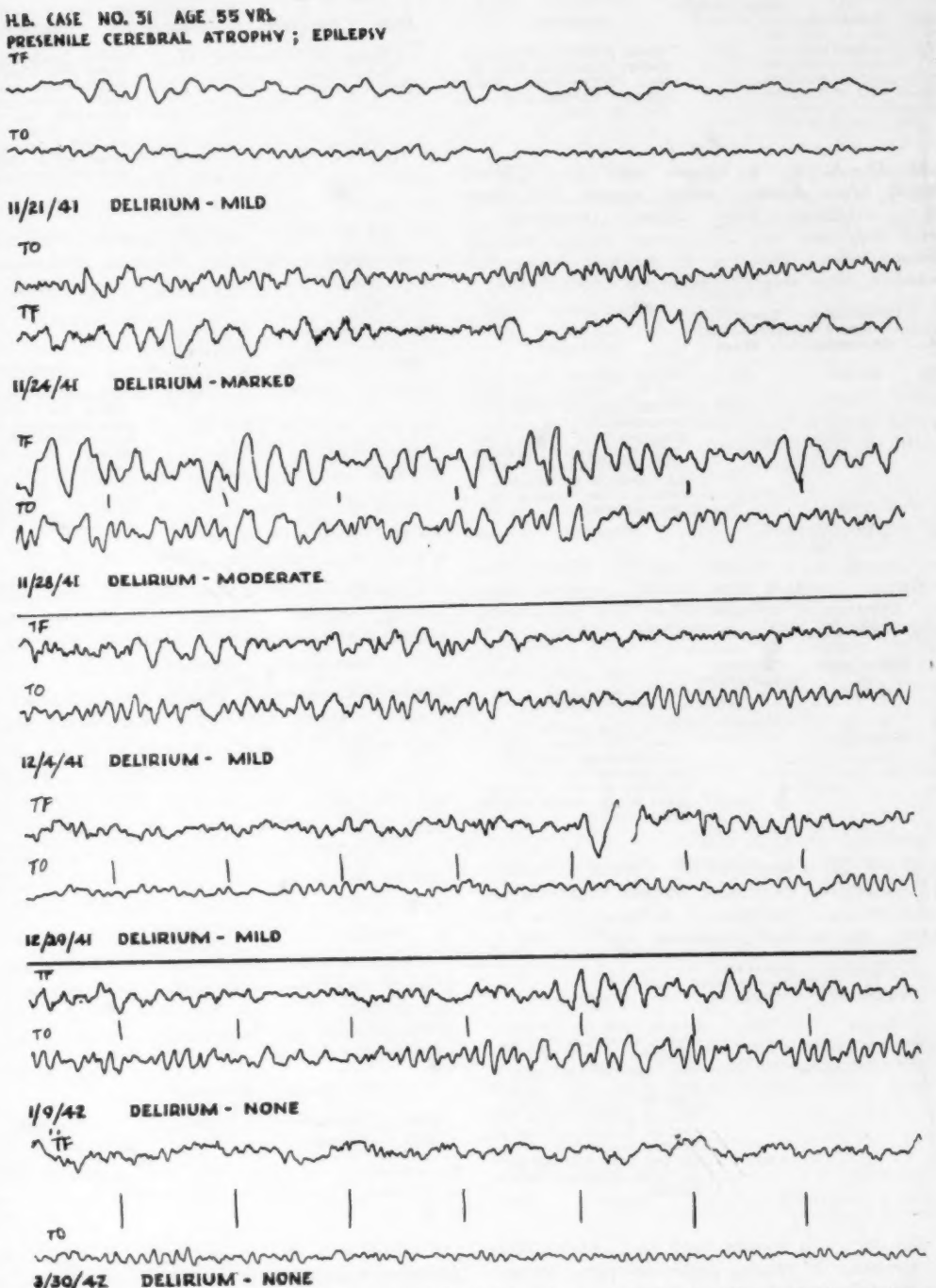

Fig. 7.—Focal abnormalities arising from the frontal lobes in a case of presenile cerebral atrophy with epilepsy. Disturbances in consciousness were always accompanied by abnormal electrical potentials, but the latter occasionally occurred in the absence of delirium.

CASE 34.—*M. B., a woman aged 68. Myocardial infarction; acute congestive heart failure. Duration of delirium before first examination, two weeks. Admission, Feb. 10, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/18	Severe	IV	Venous pressure 190 mm. of water; circulation time 26 sec.; Cheyne-Stokes respiration. Patient died Feb. 20, 1942

CASE 35.—*E. C., a woman aged 53. Chronic rheumatic heart disease; mitral stenosis and insufficiency; congestive heart failure; thrombosis of superior vena cava and left internal jugular and left subclavian veins. Duration of delirium before first examination, three weeks. Admission, Nov. 3, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/19/41	Severe	IV	Venous pressure, right arm, 150 mm. water, with rise to 180 mm. of water with compression of liver; circulation time 28 sec.; oxygen saturation of arterial blood 91.2%; carbon dioxide content of arterial blood, 38.04 volumes %. Patient died

CASE 36.—*R. B., a woman aged 73. Hypertensive heart disease; complete heart block; congestive heart failure. Duration of delirium before first examination, ten days. Admission, March 21, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/24/42	Severe; semistupor	IV	Venous pressure 205 mm. of water; circulation time (dehydrocholic acid) 45 sec., (potassium ferrocyanide) 46 sec.; complete heart block; heart rate 24. Death 3/25

CASE 37.—*F. A., a man aged 67. Chronic bronchitis; asthma; emphysema; pulmonary fibrosis; right and left ventricular failure. Duration of delirium before first examination, two weeks. Admission, Feb. 17, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/19/42	Severe	II-III	Venous pressure 140 mm. water, increased on compression of liver to 180 mm. water; circulation time 35 sec.; vital capacity 1,500 cc.; oxygen saturation of arterial blood 69%; carbon dioxide content of arterial blood 65.3 volumes %; red cells 6,100,000 per cu. mm. Patient died 2/22/42

CASE 38.—*M. P., a woman aged 43. Chronic alcoholism; cirrhosis of liver; hypercholemia; anemia. Duration of delirium before first examination, two to three weeks. Admission, Jan. 15, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/19	Severe	IV	Deep jaundice; icteric index 80; temperature 101 F.; red blood cells 1,800,000; hemoglobin 7 Gm./100 cc. Patient died January 1942

CASE 39.—*F. G., a man aged 84. Obstructive jaundice; acute left ventricular failure. Duration of delirium before first examination, two weeks. Admission, Jan. 2, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/9/42	Severe	IV	Intense jaundice; icteric index 108; Cheyne-Stokes respiration; congestive heart failure present on admission, but not at time of examination. Patient discharged to home for incurables and died shortly thereafter

CASE 40.—*E. D., a woman aged 60. Congenital polycystic kidneys; uremia. Duration of delirium before first examination, one to two weeks. Admission, Nov. 28, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/3/41	Severe	IV-V	Early signs of impending uremia for 6 mo.; Kussmaul breathing for 5-6 days; nonprotein nitrogen 286 mg./100 cc. carbon dioxide content of arterial blood 23.6 vols.%; hemoglobin 7.5 Gm./100 cc.; blood pressure 180/110. Patient died

CASE 41.—*D. B., a man aged 33. Malignant hypertension; uremia. Duration of delirium before first examination, four weeks. Admission, Nov. 23, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/27	Severe; stupor	IV	Hypertension for 3 yr.; headache and vomiting 4 wk.; six convulsions on 11/24/41; blood pressure 230/160; cerebrospinal fluid pressure 600 mm. of water; fluid xanthochromic; total protein content 120 mg./100 cc. Urine: specific gravity 1.009; albumin 4+; many red cells; urea nitrogen of blood 61 mg./100 cc. Patient died 11/30

CASE 42.—*J. N., a man aged 76. Pneumonia, lower lobe of right lung; empyema; bacteremia (Pneumococcus type IV); chronic alcoholism. Duration of delirium before first examination unknown. Admission, March 20, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/23	Severe	IV	Temperature 102 F.; oxygen saturation of arterial blood 95.6/100 cc. Patient died

CASE 43.—*O. M., a man aged 72. Myocardial infarction; hemiplegia of embolic origin. (?) Duration of delirium before first examination, two to three weeks. Admission, Feb. 1, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/24	Severe	IV	Cheyne-Stokes respiration; oxygen saturation of arterial blood, apneic phase, 91.7%; dyspneic phase, 94.5%. Patient died

CASE 44.—*J. C., a woman aged 46. Previous bilateral mastectomy; carcinoma of breast, with metastases to skin, lymph nodes, lung, pleura and brain (?); severe emaciation. Duration of delirium before first examination, two months. Admission, Oct. 28, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/29	Moderate	II	Formed visual hallucinations; dyspnea; vital capacity 1,000 cc. Patient died 10/31/41

All but 1 of the patients in group 5 had pronounced disturbances in the level of awareness. The exception (J. C., case 44) became stuporous shortly after the examination. Nine of the 11 patients showed stage IV electroencephalograms, and the remaining 2 patients, stage III and stage II electroencephalograms respectively. Although all these patients died shortly after examination, the 4 patients for whom it was determined showed some degree of reversibility of the electroencephalogram with administration of oxygen and during the phasic changes of Cheyne-Stokes respiration. These reversible changes will be discussed in another paper.[13] As indicated previously, electroencephalographic changes of stage IV need not be irreversible, although it is always associated with the more severe disturbances in awareness.

Although postmortem examination was performed on 13 of the 16 patients of the total series, it is not our purpose in this paper to discuss the histologic changes in the brain. Moreover, in many instances death occurred some time after the period of clinical study. Further, the neuropathologic examination was not adequate for careful evaluation. In 1 patient, however (group 3, case 25, with a diagnosis of dermatomyositis), the brain showed minute focal areas of gliosis, probably secondary to disease of the smaller vessels, which undoubtedly had been present to some degree at the time of clinical study.

Group VI.—These 9 patients who experienced varying degrees of delirium were examined once. Circumstances beyond our control prevented reexamination.

CASE 45.—*H. W., a woman aged 73. Arteriosclerotic heart disease; previous myocardial infarction; chronic congestive heart failure (four years). Duration of delirium before first examination unknown. Admission, Oct. 27, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/29	Moderate	V	Venous pressure 170 mm. of water, with increase on compression of liver to 300 mm.; circulation time 52 sec.

13. Engel, G. L., and Romano, J.: Studies of Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, Arch. Neurol. & Psychiat., this issue, p. 378.

CASE 46.—*M. H., a man aged 64. Coronary occlusion; congestive heart failure. Duration of delirium before first examination, three weeks. Admission, March 19, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/10	Mild	I-II	Delirium more severe during first 10 days of hospitalization, greatly improved on 4/10/42. Venous pressure 85 mm. of water; circulation time 25 sec.; oxygen saturation of arterial blood 98%

CASE 47.—*C. W., a man 71. Arteriosclerotic heart disease; congestive heart failure. Duration of delirium before first examination, six weeks (?). Admission, Sept. 25, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/8	Severe	II	Cheyne-Stokes respiration; circulation time 15 sec.

CASE 48.—*B. K., a man aged 64. Chronic bronchitis; asthma; emphysema. Duration of delirium before first examination unknown. Admission, Oct. 11, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/17/41	Moderate	IV-V	Oxygen saturation of arterial blood 86%

CASE 49.—*G. Y., a man aged 67. Chronic bronchitis; asthma; emphysema; acute infection of upper respiratory tract. Duration of delirium before first examination, two days. Admission, Dec. 21, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/23/41	Mild	II	Patient recovering from severe acute attack of asthma

CASE 50.—*F. S., a man aged 61. Asthma; bronchitis; emphysema. Duration of delirium before first examination unknown. Admission, Dec. 2, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/8	Mild	I	Oxygen saturation of arterial blood, 78%

CASE 51.—*B. F., a man aged 65. Asthma; bronchitis; emphysema; bilateral bronchopneumonia. Duration of delirium before first examination, three weeks. Admission Feb. 25, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/10	Moderate	I	Progressive clinical improvement in week preceding study

CASE 52.—*J. F., a man aged 57. Chronic alcoholism; gastritis. Duration of delirium before first examination, two months. Admission Feb. 23, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/26	Moderate	III (?)	Excessive drinking for past 2 mo.; history of addiction to alcohol for 20 yr. or more

CASE 53.—*J. T., a man aged 38. Chronic alcoholism (?); head trauma. Duration of delirium before first examination unknown. Admission, Oct. 13, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/14	Severe	III	Comatose state on admission, but patient more aware, active and delirious during examination

The correlation between age and course of illness for the 53 patients may be noted. Fifteen patients were between the ages of 13 and 50; 11 patients, between 50 and 60; 17 patients, between 60 and 70, and 10 patients were more than 70. Forty-one patients were studied long enough for the eventual outcome to be established. Of the 12 patients who recovered completely, or nearly completely, 7 were less than 50 years of age. In contrast, of the 29 patients who recovered partially (group 2), who failed to improve (group 3) or who died (group 5), only 7 were less than 50 years of age.

COMMENT

The data presented demonstrate that delirium as defined in this paper is associated with an electrical disturbance of the brain which may be reversible to the extent that the delirium is reversible. Additional data, which will be discussed in more detail in an accompanying report,[13] have also indicated that the electrical abnormality may be favorably influenced more specifically by supply of missing metabolic elements, such as oxygen, dextrose, blood or adrenal cortex extract.

The electrical abnormalities observed are consistent with changes to be expected when the basic integrity of the nerve cell and its environment are disturbed. These abnormalities include, in order of intensity: (1) decrease in frequency, (2) disorganization and (3) reorganization at a lower energy level. Decrease in frequency implies decreasing levels of or decreasing responses to cortical excitation, which, in turn, may be due to a decrease in the metabolic activities of the neurons or to a decrease in the effect of afferent impulses to the cortex, such as occurs normally in sleep. Disorganization implies a disturbance in the synchronizing or pace-making mechanisms and would be expected to represent a more pronounced response to a noxious factor acting diffusely. With the continuation of the process the pattern tends to reorganize at a slower frequency with higher amplitude, i. e., at a lower energy level. Thus, stages I and II might represent the first phase; stages III and IV, the phase of disorganization, and stage V, the phase of reorganization at a lower energy level. The diminished effect of afferent impulses on the electrical pattern in the late phases is demonstrated by the lack of effect on stages III, IV and V of opening and closing the eyes. Any of these stages were reversible. In certain instances in which the electroencephalogram had returned to normal, the psychologic status of the patient revealed some degree of intellectual deficit. This minimal dementia is possibly due to the complete destruction of certain nerve cells while the essential electrical pattern of the remaining cells returns to normal. Recent observations have revealed a number of patients with long-standing dementia of gradual development and with cortical atrophy, demonstrated pneumoencephalographically, whose electroencephalograms were entirely normal.[14] These data support the view that the abnormal electrical activity arises from damaged or dying cells. The intensity and reversibility of the electrical disturbance were directly correlated with the speed of onset, the intensity and duration of the noxious stimulus and the basic premorbid integrity of the central nervous system, particularly as it was influenced by factors of age, nutritive state and circulatory efficiency.

It is noteworthy that these electroencephalographic changes are essentially the same as those which have previously been reported in association with acute and chronic cerebral trauma,[15] encephalitis,[5a] neurosyphilis,[5f] increased intracranial pressure,[5e] hypoglycemia,[4d] the administration of certain drugs which influence consciousness [4e] and certain focal cerebral lesions which are reversible. Further, we have observed essentially the same electroencephalographic stages in a condensed form during syncope and as a result of a variety of causes.[16] These data obtained by independent observers offer further evidence of the nonspecificity of these electroencephalographic changes.

The relation of these electroencephalographic changes to epilepsy is not clear to us. Five of our patients had convulsions more than once. Three patients had convulsions antedating the delirious episodes (H. B., case 31; E. M., case 9, and H. C., case 3). For at least 1 of these 3 patients (H. C., case 3) the interseizure record was unmistakably diagnostic of epilepsy (wave and spike pattern) at a time when no disturbance in behavior was demonstrable, while the delirious episodes of the other 2 patients were directly associated with the seizures. The fourth and fifth patients (W. F., case 26, and D. B., case 41) both had repeated seizures during late stages of malignant hypertension but had no past or family history of epilepsy. During the epi-

14. Engel, G. L.: Unpublished data.

15. Jasper and others.[5b] Williams, footnote 5 *c* and 5 *d*.

16. Engel, G. L.; Romano, J., and McLin, T.: Vasodepressor and Carotid Sinus Syncope: Clinical, Electroencephalographic and Electrocardiographic Observations, Arch. Int. Med., to be published.

sodes of delirium it was not possible to differentiate the records of these 5 patients from those of any other delirious patients. Williams [5c] was unable to predict the development of post-traumatic epilepsy from the appearance of the electroencephalograms obtained after acute injuries to the head.

Analysis of the psychologic data reveals a direct correlation between the electrical abnormality and the primary psychologic symptom in delirium, i. e., the disturbance of consciousness. There was far less correlation between the electrical abnormality and the more personal aspects of behavior, namely, the character and expression of anxiety, the content of thought and the nature of sense deceptions. It must be emphasized that while this correlation with disturbances in consciousness was clear, the mere coincidence of these psychologic disturbances and electroencephalographic abnormalities does not in itself establish a cause and effect relation. More complete knowledge of the basic mechanisms responsible for normal and abnormal electrical activity must be acquired before conclusions are drawn concerning the association of characteristic electrical patterns with various types of psychologic behavior. Furthermore, we believe that in future electroencephalographic studies of patients with psychologic disturbances the presence or absence of disturbances in consciousness must be considered before other correlations with behavior are attempted. The mere presence of abnormal brain waves in the electroencephalogram of a person with disturbances of behavior does not establish a relation between the two. In a case of epilepsy, for example, the abnormal record of the interseizure period may be unassociated with any disturbances in behavior, while the immediately postseizure period may be accompanied by conspicuous disturbances in consciousness and confusion.

From a clinical point of view, there is usually no need to utilize the electroencephalogram in the diagnosis of delirium. Simple psychologic tests, designed to evaluate the awareness or attention of a patient, are adequate. However, the method may be of aid in clinical confirmation, in evaluation of the degree of physiologic restoration and in following the course of specific therapy. Further, the method has great value in experimental physiologic studies of spontaneous and induced deliriums.

SUMMARY

Psychologic and electroencephalographic studies of 53 patients with delirium of varying cause, intensity and duration revealed electroencephalographic abnormalities in all patients who had disturbances in consciousness. These changes were found to be reversible to the extent to which the clinical delirium was reversible. The character of the electroencephalographic change appeared to be independent of the specific underlying disease process but was directly related to the intensity, duration and reversibility of the noxious factors, as modified by the basic physiologic status of the body. A correlation was established between the electrical abnormality and the primary psychologic symptom in delirium, i. e., the disturbance of consciousness, but there was far less correlation with the more personal aspects of behavior, namely, the character and expression of anxiety, the content of thought and the nature of sense deceptions.

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DELIRIUM

II. REVERSIBILITY OF THE ELECTROENCEPHALOGRAM WITH EXPERIMENTAL PROCEDURES

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CINCINNATI

The electroencephalographic changes associated with delirium have been presented in a previous report.[1] These changes were observed to be reversible to the extent to which the delirium was reversible. The character of the electroencephalographic changes was determined by the intensity, duration and reversibility of action of the noxious factors as modified by the essential premorbid integrity of the central nervous system.

In this report further data will be presented to illustrate the reversibility of the electroencephalogram during experimental procedures designed to modify some of the basic physiologic derangements. The effects studied included those of (*a*) inhalation of oxygen, (*b*) changes in posture, (*c*) phases of Cheyne-Stokes respiration, (*d*) blood transfusion, (*e*) administration of adrenal cortex substances and (*f*) infusion of dextrose.

MATERIAL AND METHODS

Twenty-five patients were studied. Clinical and laboratory observations on these patients, as well as the psychologic and electroencephalographic methods of examination and interpretation, are presented in a previous report.[1]

The method of quantitative analysis of the electroencephalogram and the classification of the degrees of electrical abnormality as stages I to V have already been described.[1] These five stages may again be summarized.

Stage I: Predominance of normal, regular frequencies with a small amount of regular and irregular slow frequencies (5 to 7 per second). There is generally some decrease in regularity of the record as a whole.

Stage II: Further decrease in regularity of the entire record, which now contains only a moderate amount of normal, regular frequencies. There is an increase both in low voltage fast activity and in regular and irregular slow (4 to 7 per second) frequencies.

Stage III: Predominantly low voltage fast activity with some regular and irregular slow frequencies (3 to 6 per second) and relatively little activity in the normal range of frequencies.

Stage IV: Completely disorganized, irregular record with a dominant slow pattern (2 to 7 per second), variable small amounts of low voltage fast activity and no recognizable alpha activity (8 to 12 per second). At this stage the record frequently shows groups of high voltage very slow waves (½ to 3 per second) recurring in a rhythmic fashion. Low voltage fast activity is sometimes superimposed on these slow waves.

Stage V: Rather regular slow activity (3 to 7 per second) of moderately high voltage with few or no normal frequencies.

Stages III, IV and V are not influenced by the subject's opening or closing the eyes.

In addition, as further criteria for comparison of consecutive tracings under different conditions, the total amount of 8 to 12 per second activity and the dominant frequency of each record were noted. The dominant frequency was the frequency representing 50 per cent or more of the total record. When no frequency accounted for 50 per cent of the record, the most common frequencies which together made up 60 per cent of the total were taken as dominant.

The following arbitrary criteria were used as measures of the significance of the changes observed in the electroencephalogram during the experimental procedures:

1. The change in the electroencephalographic pattern was considered definitely significant when two or more of the following features were present: (*a*) change in stage, (*b*) shift in dominant frequency or (*c*) a change of more than 20 in the percentage of 8 to 12 per second activity.

2. The alteration in the electroencephalographic pattern was regarded as probably significant when the following features were present: (*a*) no change in stage, but (*b*) a shift in dominant frequency and (*c*) a change of from 10 to 20 in the percentage of 8 to 12 per second activity.

3. A shift in dominant frequency alone, a change in the total amount of 8 to 12 per second activity alone or a shift in dominant frequency with a change of less than 10 in the percentage of 8 to 12 per second activity were considered as not significant.

INHALATION OF OXYGEN

Experimental Results. — Electroencephalographic tracings were taken in a total of 20 experiments before, during and occasionally after oxygen was administered by mask to 9 patients with cardiac decompensation and to 4 patients with pulmonary decompensation. The results

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1. Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, Arch. Neurol. & Psychiat., this issue, p. 356.

are recorded in table 1 and typical cases are illustrated in figures 1 and 2.

According to the criteria of change already outlined, the electroencephalogram showed definite improvement in 10 experiments, probable improvement in 7 experiments and no improvement in 3 experiments.

Of the patients showing definite improvement, 5 had cardiac failure (6 experiments) and 3 chronic pulmonary disease (4 experiments). Three determinations of the oxygen and carbon dioxide contents of arterial blood were made on the patients with heart disease and 4 determinations on the 3 with pulmonary disease. All the patients with cardiac decompensation had normal values for oxygen saturation [2] (96, 93.7 and 95.5 per cent) and carbon dioxide content (43.22, 39.9 and 48.1 volumes per cent respectively) of arterial blood. In all patients inhalation of 100 per cent oxygen resulted in an increase in oxygen saturation of arterial blood to above normal (103, 104 and 105 per cent respectively), while in 2 patients the carbon dioxide content of arterial blood fell slightly and in 1 it was unchanged. In all the patients with pulmonary disease who showed definite improvement in the electroencephalographic pattern the oxygen saturation of arterial blood was below normal (69, 71.4, 87.3 and 88.5 per cent), while the carbon dioxide content was high (62.6, 58.2, 54.1 and 55.5 volumes per cent). In all these patients the oxygen saturation of arterial blood rose to normal or above normal during inhalation of oxygen while in 2 patients

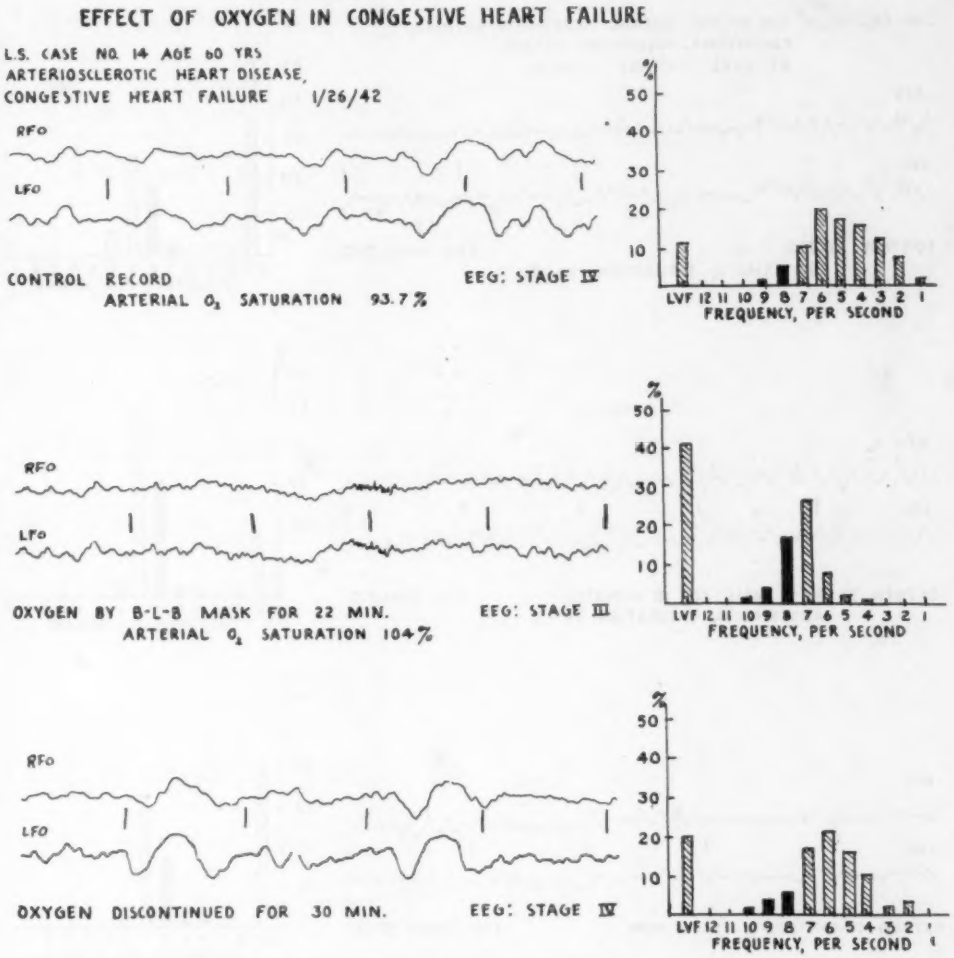

Fig. 1.—The electroencephalogram shifted from stage IV to stage III during administration of oxygen and then returned to stage IV thirty minutes after the use of oxygen was discontinued. The spectrum analysis of three hundred second samples is presented on the right. The oxygen saturation of arterial blood was 93.7 per cent during the first run and 104 per cent during administration of oxygen.

2. The values were not corrected for the amount of oxygen dissolved in the plasma. Oxygen saturations of arterial blood of over 100 per cent may result when this correction is not made. Since oxygen dissolved in plasma is available for metabolic needs, it is properly included in studies of this nature.

the carbon dioxide content rose slightly and in 1 it was unchanged (table 1).

Of the 10 electroencephalograms (obtained from 8 patients) showing definite improvement during administration of oxygen, 4 represented stage IV before inhalation of oxygen; 1, stage III; 3, stage III to stage II; 1, stage II, and 1, stage II to I. The electroencephalograms of 5 of these 8 patients showed partial or complete restoration to normal with recovery from the acute disease process. The electroencephalogram of 1 patient changed from stage IV to stage V, and a considerable degree of dementia persisted. The 2 remaining patients were examined only once.

In 7 experiments on 5 patients the improvement in the electroencephalographic pattern was considered to be of probable, but not definite, significance. Four patients had congestive heart failure. Two patients (K. T., case 2, and J. Mc., case 27) had each shown definite improvement in the electroencephalogram on one other occasion—K. T. at stage IV, but to a less striking degree at stages II and I. J. Mc. showed decreasing improvement as the electroencephalogram shifted toward stage V. Arterial blood was studied in 4 experiments. Oxygen saturation was normal in 3 determinations and low (80 per cent) in 1 determination. With inhalation of oxygen it rose to 98 per cent or above in all instances. The carbon dioxide contents of arterial blood were not remarkable and showed no significant changes. The electroencephalograms before the administration of oxygen represented stage IV in 3 experiments and stage V, stage II and stage I respectively in 1 experiment each.

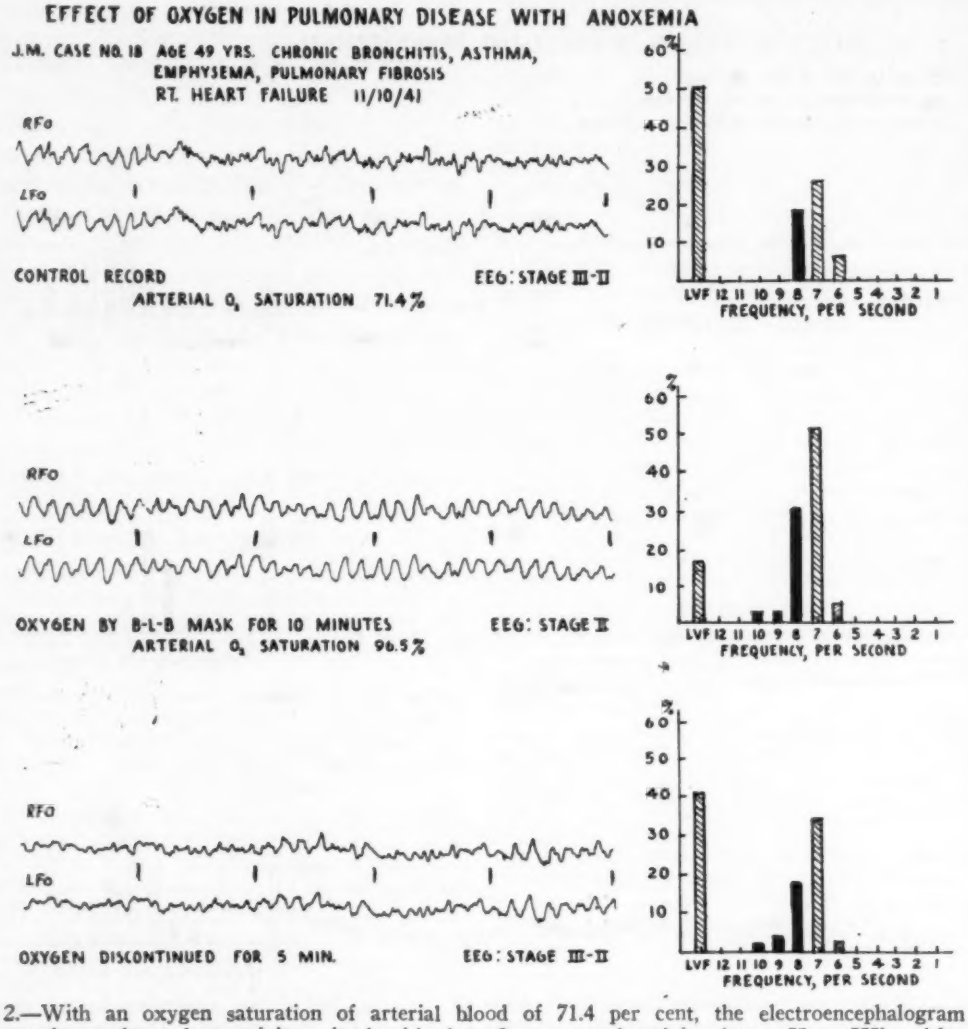

Fig. 2.—With an oxygen saturation of arterial blood of 71.4 per cent, the electroencephalogram showed predominant low voltage fast activity mixed with 6 to 8 per second activity (stage II to III). After oxygen was inhaled for ten minutes, the oxygen saturation of arterial blood rose to 96.5 per cent, and the electroencephalogram showed dominant 7 per second activity (stage II). With interruption of inhalation of oxygen, the record returned toward the original pattern.

TABLE 1.—*Effect of Administration of Oxygen in Cases of Congestive Heart Failure and Pulmonary Insufficiency on the Electroencephalogram*

Name, Sex, Age, Yr.	Case No.	Diagnosis	Date	Electroencephalogram: Stage			Electroencephalogram: Percentage of Frequency, 8-12/Sec.			Electroencephalogram: Dominant Frequency/Sec.*			Arterial Oxygen Saturation, %		Arterial Carbon Dioxide Content, Vol. %		Electroencephalographic Improvement	Comment
				Before	During	After	Before	During	After	Before	During	After	Before	During	Before	During		
L. S. M 60	14	Arteriosclerotic heart disease; congestive heart failure	1/20	IV	III	..	6	25	..	5-7 LVF	LVF	...	96.0	103	43.2	41.5	Definite	
			1/26	IV	III	IV	6	22	10	3-6	LVF 7	5-7 LVF	93.7	104	39.9	37.4	Definite	
C. W. M 71	47	Arteriosclerotic heart disease; congestive heart failure	10/8	II	I	..	37	67	..	7-8	8-9	...	....	...	....	....	Definite	Moderately severe left ventricular failure; Cheyne-Stokes respiration
W. F. M 54	15	Acute coronary occlusion; congestive heart failure	10/2	III	III-II	..	20	44	..	LVF 7	7-8 LVF	...	....	...	....	....	Definite	Severe congestive heart failure; Cheyne-Stokes respiration
K. T. F 61	2	Hypertensive heart disease; congestive heart failure	12/29	IV	IV	..	17	39	..	2-7	6-8 LVF	...	....	...	....	....	Definite	Moderately severe left ventricular failure
			1/5	II	II-I	..	38	50	..	6-8	7-9	...	....	...	....	....	Probable	Minimal left ventricular failure
			1/7	I	I	..	56	69	..	8-9 LVF	8-9	...	....	...	....	....	Probable	Minimal left ventricular failure
J. Mc. M 74	27	Congestive heart failure; pneumonia; empyema; cirrhosis of liver; jaundice	12/24	IV	IV	IV	9	23	25	4-7	6-8	6-8	94.2	...	45.1	....	Probable	Severe left and right ventricular failure; jaundice
			12/30	IV	V	V	7	33	25	5-7	7-8	6-8	95.5	105	48.1	48.1	Definite	Heart failure less severe; jaundice less; empyema
			1/15	V	V	..	15	28	..	5-7	6-8	...	94.7	105	48.7	48.7	Probable	Moderately severe congestive heart failure; empyema; jaundice
E. C. F 53	35	Rheumatic heart disease; mitral stenosis and mitral insufficiency; congestive heart failure; thrombosis of superior vena cava, left internal jugular and left subclavian veins	11/19	IV	IV	..	3	14	..	3-6	6-8	...	91.2	99.3	38.0	38.1	Probable	
A. C. F 55	13	Hypertensive heart disease; congestive heart failure	4/27	IV	IV	..	9	20	..	5-7	6-8	...	80.0	98.2	49.6	51.5	Probable	Before inhalation: arterial-internal jugular venous oxygen difference 8.52 vol. %. During inhalation: arterial-internal jugular venous oxygen difference 12.66 vol. %
S. F. F 54	24	Rheumatic heart disease; chronic congestive heart failure	1/6	V	V	..	30	33	..	6-8	7-8	...	....	...	....	....	None	Severe failure
R. B. F 73	36	Hypertensive heart disease; complete heart block; congestive heart failure	3/24	IV	IV	..	0	0	..	3-4	4-5	...	....	...	....	....	None	Venous pressure 205 mm. water; circulation time 45 sec.
E. A. M 67	37	Chronic bronchitis; asthma; emphysema; right and left ventricular failure	2/19	III-II	II	..	12	34	..	6-7	7-8	...	69.0	...	62.6	....	Definite	Arterial-internal jugular venous oxygen difference 2.86 vol. %; internal jugular venous carbon dioxide content 65.3 vol. %
G. A. M 60	19	Chronic bronchitis; asthma; emphysema; right ventricular failure	12/3	III	III	..	43	42	..	LVF	LVF	...	79.0	101.0	59.2	59.6	None	Arterial-internal jugular venous oxygen difference 5.45 vol. %
			12/16	III-II	II	II	43	80	34	6-9	8-10	6-9	87.3	101.8	54.1	53.5	Definite	
			12/19	II-I	I	..	66	83	..	7-9	9-10	...	88.5	101.0	55.5	57.6	Definite	
J. M. M 49	18	Chronic bronchitis; asthma; emphysema; pulmonary fibrosis; failure of right side of heart	11/10	III-II	II	III-II	18	32	23	LVF	7-8	LVF, 7	71.4	96.5	58.2	60.0	Definite	
B. K. M 64	48	Chronic bronchitis; asthma; emphysema	10/17	IV-V	IV-V	..	16	27	..	6-7	6-8	...	86.8	...	....	....	Probable	

* In this table, and in the accompanying tables, LVF indicates low voltage fast activity.

The fifth patient of the group who showed probable improvement in the electroencephalogram had chronic pulmonary disease and at the time of study had mild anoxemia (oxygen saturation arterial of blood 86.8 per cent). The electroencephalogram was of stage IV to stage V type. Inhalation of oxygen resulted in some increase in the amount of 8 to 12 per second activity and a slight shift toward a faster dominant frequency. This patient was examined only once.

Inhalation of oxygen failed to affect the electroencephalograms of 3 patients. Two of these patients had congestive heart failure. One of them was semistuporous at the time of examination; the electroencephalogram was of extreme stage IV type, and the patient died the following day. The second patient had chronic congestive heart failure, and the degree of disturbance in the level of awareness was essentially unchanged since the first examination, four months earlier. The electroencephalogram was of stage V type. No studies in the gases of the blood were carried out on these 2 patients. The third patient (G. A., case 19) had pulmonary disease. He had a stage III electroencephalogram on first examination, and the oxygen saturation of arterial blood rose from 79 to 101 per cent during the inhalation of oxygen. On two subsequent occasions inhalation of oxygen resulted in definite improvement in the electroencephalogram. It is possible that the criteria necessary to show changes within stage III (dominant low voltage fast activity) are inadequate.

Because of the presence of the oxygen mask, it was not possible to test the mental status during inhalation of oxygen. However, in many instances it was obvious that the patient was brighter and more alert immediately after the mask was removed.

Summary.—During the administration of oxygen to 9 patients with congestive heart failure and to 4 patients with pulmonary decompensation (20 experiments), the electroencephalogram showed definite improvement in 10 experiments probable improvement in 7 experiments and no significant change in 3 experiments. The patients with congestive heart failure showed electroencephalographic improvement in spite of the fact that the oxygen saturation of arterial blood was normal before administration of oxygen. However, these patients generally showed a rise in oxygen saturation to over 100 per cent. The patients with chronic pulmonary disease all had cyanosis and anoxemia, and administration of oxygen raised the oxygen saturation of arterial blood to normal levels or higher. Improvement was demonstrable at all stages (I to V) of the electroencephalogram but was least noticeable at stage V. On the whole, the improvement during administration of oxygen was greatest for patients whose delirium was of recent origin and who showed eventual restoration to normal, or near normal, of both the electroencephalogram and the mental status. The changes occurring in the electroencephalogram during use of oxygen were identical with those appearing spontaneously some days or weeks later, during the course of recovery from the underlying disease.

TABLE 2.—*Effect of Posture in Cases of Congestive Heart Failure on the Electroencephalogram*

Name, Sex, Age, Yr.	Case No.	Diagnosis	Date	Electroencephalogram: Sitting Position: Stage	Sitting Position: Percentage 8-12 per Sec. Frequency	Sitting Position: Dominant Frequency	Recumbent Position: Stage	Recumbent Position: Percentage 8-12 per Sec. Frequency	Recumbent Position: Dominant Frequency	Comment
L. S. M 60	14	Arteriosclerotic heart disease; congestive heart failure	1/20	III	13	LVF	IV	6	5-7 per sec. LVF	Patient recumbent 18 min. circulation time 53 sec. (dehydrocholic acid); venous pressure 180 mm. of water, with rise on compression of right upper quadrant to 230 mm.
W. F. M 54	15	Acute coronary occlusion; congestive heart failure	10/2	III	22	LVF	IV	20	LVF 5-7 per sec.	Patient recumbent 30 min.; circulation time 43 sec. (dehydrocholic acid); venous pressure 180 mm. of water
H. W. F 73	45	Arteriosclerotic heart disease; chronic congestive heart failure	10/29	V	31	6-8 per sec.	V	22	7-8 per sec.	Patient recumbent 7 min.; circulation time 52 sec. (dehydrocholic acid); venous pressure 170 mm. of water, with rise on compression of right upper quadrant to 300 mm. of water

CHANGES IN POSTURE

Because patients with congestive heart failure become more dyspneic and cyanotic when recumbent than when sitting, the effect on the electro-

encephalogram of changes in posture was studied in 3 such patients. The results are summarized in table 2, and a typical case is illustrated in figure 3. All the patients had severe congestive heart failure at the time of study, as was evidenced by prolonged circulation time and high venous pressure. In 2 instances after the patients had been recumbent for eighteen to thirty minutes, the electroencephalogram became definitely more abnormal. Both patients had stage III electroencephalograms when they were sitting, which shifted to stage IV patterns when they were recumbent. The electroencephalogram of the third patient showed a moderate change in a similar direction with a postural change of seven minutes' duration. This patient had chronic heart failure, and the electroencephalogram represented stage V, the phase of chronic damage. All 3 patients were obviously more dyspneic, cyanotic and uncomfortable in the recumbent position; the mental statuses in the two positions were not compared.

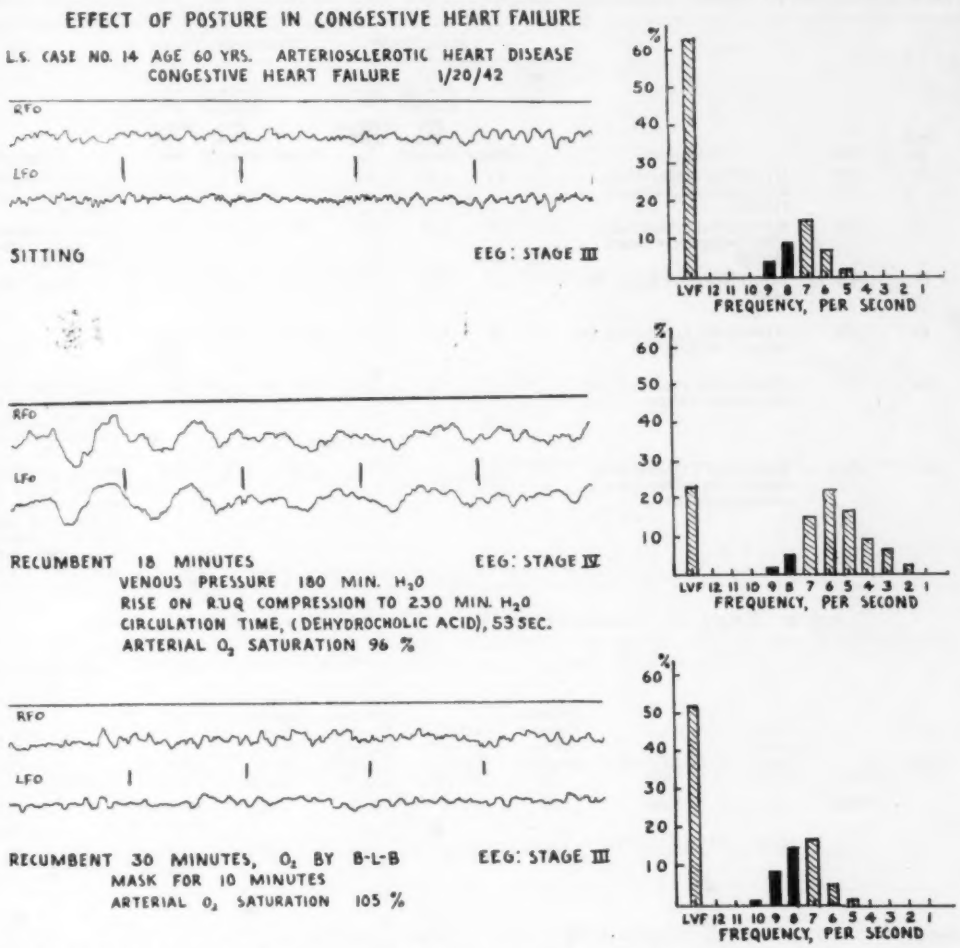

Fig. 3.—After the patient had been eighteen minutes in the recumbent position, the electroencephalogram shifted to stage IV, from the control phase of stage III when he was in the sitting position. Administration of oxygen, with the patient in the recumbent position, led to improvement in the electroencephalogram (stage III).

PHASIC CHANGES ASSOCIATED WITH CHEYNE-STOKES RESPIRATION

All clinicians are familiar with the patient with Cheyne-Stokes respiration who fluctuates between stupor and confused agitation during the phasic changes in respiration. It is of interest to study the electroencephalogram during these fluctuations. Electroencephalographic studies were made on 6 patients with Cheyne-Stokes respiration during the alternating phases of respiration (table 3). A total run of three hundred seconds of electroencephalographic record was analyzed for each phase. A typical complete cycle is illustrated in figure 4.

With 4 patients the electroencephalograms showed a definite and significant difference for the two respiratory phases, shifting toward a

more normal pattern in the hyperpneic phase and reversing to a more abnormal one in the apneic phase. All these patients had cardiac disease: Three had moderate congestive heart failure, and 1 was recovering from congestive heart failure at the time of examination. Three of the patients had stage IV electroencephalograms, and 1 had a stage II encephalogram during the apneic phase.

Two patients showed no significant difference in the electroencephalograms taken during the two phases of Cheyne-Stokes respiration. One patient had obstructive jaundice and hypercholemia and had recovered from congestive heart failure. The second patient had malignant hypertension and uremia. Both had stage IV electroencephalograms, and it is perhaps significant that the records for both showed extremely slow dominant frequencies and no (0 to 3 per cent) frequencies in the 8 to 12 per second range.

All 6 patients showed obvious fluctuations in awareness during the alternating phases of respirations. However both the changes in the level of consciousness and the alterations in the electroencephalogram appeared to lag somewhat behind the changes in respiration. This is clear on gross inspection of figure 4, in which the beginning restlessness is marked by the superimposition of muscle potentials on the electroencephalogram. This lag suggests that both the changes in cortical potentials and those in consciousness are secondary to the alterations in respiration. It explains, perhaps, our failure to demonstrate a difference in spectrum analyses between the hyperpneic and the apneic phase in the 2 patients with the most abnormal electroencephalograms.

TABLE 3.—*Effects of Phasic Changes of Cheyne-Stokes Respiration on the Electroencephalogram*

Name; Sex; Age, Yr.	Case No.	Date	Diagnosis	Apneic Phase: Stage	Apneic Phase: Percentage 8-12 per Sec. Frequency	Apneic Phase: Dominant Frequency (per Sec.)	Hyperpneic Phase: Stage	Hyperpneic Phase: Percentage 8-12 per Sec. Frequency	Hyperpneic Phase: Dominant Frequency (per Sec.)	Comment
M. B. F 68	34	2/17	Myocardial infarction; acute congestive heart failure	IV	6	5-6	IV	27	6-8	Venous pressure 190 mm. of water; circulation time 26 sec.
W. F. M 54	15	10/2	Myocardial infarction; acute congestive heart failure	IV	23	5-7	II	42	7-8	Venous pressure 180 mm. of water; circulation time 43 sec.
C. W. M 71	47	10/8	Arteriosclerotic heart disease	II	37	6-8	II-I	58	7-8	Circulation time 15 sec.
O. M. M 72	43	2/24	Myocardial infarction; embolic (?) hemiplegia	IV	17	5-7	III-II	42	7-8 and LVF	
F. G. M 84	39	1/9	Obstructive jaundice; left ventricular failure	IV	3	4-6	IV	1	2-5	Congestive heart failure on admission (1/2/42) but not at time of examination; icteric index 108
W. F. M 46	26	1/19	Malignant hypertension; uremia; hypertensive encephalopathy	IV	0	2-4	IV	0	3-5	Blood pressure 240/165; cerebrospinal fluid pressure 410 mm. of water; nonprotein nitrogen of blood 73 mg./100 cc.; venous pressure elevated; pulmonary congestion

TABLE 4.—*Effect of Transfusion of Whole Blood in a Case of Severe Anemia*

Name; Sex; Age, Yr.	Case No.	Date	Hemoglobin, Gm./100 Cc.	Red Blood Cells	Arterial Oxygen Saturation, %	Arterial Oxygen Content, Vol. %	Internal Jugular Venous Oxygen Content, Vol. %	Arteriovenous Oxygen, Difference, Vol. %	Mental Status	Electroencephalogram: Stage	Electroencephalogram: Percentage 8-12 per Sec. Frequency	Electroencephalogram: Dominant Frequency (per Sec.)
A. P. F 74	4	4/ 9/42	2.5	630,000	100	5.30	2.65	2.65	Moderate confusion	II	11	6-7
		4/11/42	5.8	1,660,000	102	10.03	5.62	4.41	Mild confusion	I to normal	72	8

Since 1 of these patients (W. F., case 26) subsequently improved clinically (although he eventually died), lack of essential reversibility cannot be invoked as the explanation.

BLOOD TRANSFUSION

In chronic anemia due to inadequate hematopoiesis [3] or to chronic loss of blood without other

3. Pernicious anemia obviously cannot be included with these anemias, since there is much evidence that it is a deficiency disease involving more than blood formation alone. Indeed, it is well known that delirium may develop with only moderate anemia, and may even become worse while the blood count is rising.

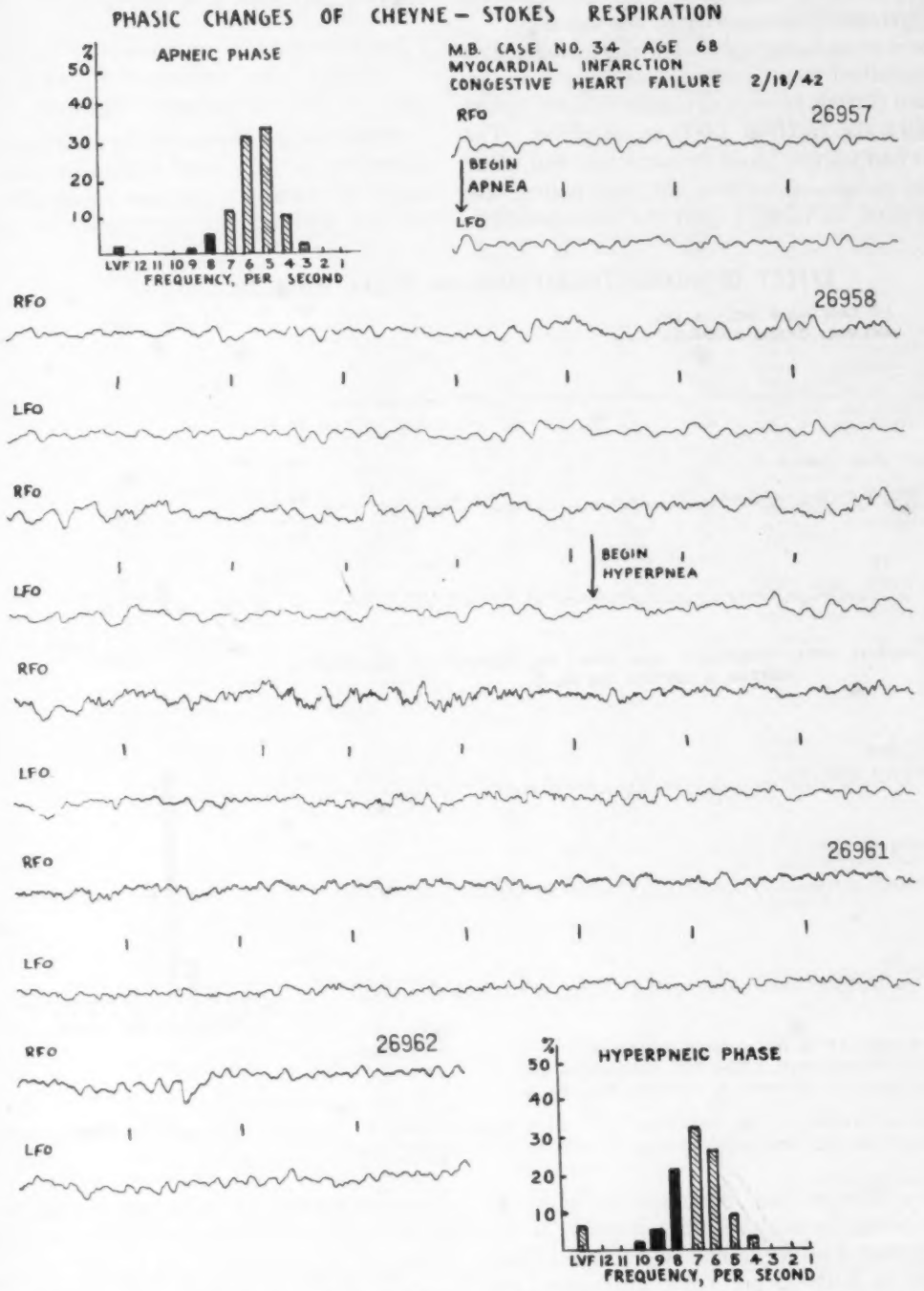

Fig. 4.—One complete respiratory cycle is illustrated, while the frequency spectrums are the result of analyses of three hundred second samples of each phase. During the apneic phase the patient was stuporous. During the hyperpneic phase she became more active, as evidenced by the appearance of muscle potentials in the electroencephalogram.

complications, the reduction in hemoglobin must be profound before the oxygen supply to the brain is impaired. Greatly increased cerebral circulation generally compensates for the reduction in oxygen-carrying capacity of the blood.

Electroencephalographic and psychologic data were obtained from a patient suffering from severe and chronic anemia, probably aplastic, before and after she received 1,000 cc. of blood. The patient had normal blood pressure and had never been in shock. The data for this patient are summarized in table 4, and the electroencephalographic changes are illustrated in figure 5. With an initial hemoglobin concentration of 2.5 Gm. per hundred cubic centimeters and a red blood cell count of 630,000 per cubic millimeter, the difference in oxygen content between arterial and internal jugular venous blood was only 2.65 volumes per cent. After a transfusion of 1,000 cc. of blood, the oxygen-carrying capacity of the blood was doubled and the arteriovenous oxygen difference increased to 4.41 volumes per cent. There was a significant improvement both in the electroencephalogram and in the mental status after this procedure. It is reasonable to ascribe this improvement to the increased oxygen-carrying capacity of the blood, since it is unlikely that the cerebral blood flow increased.

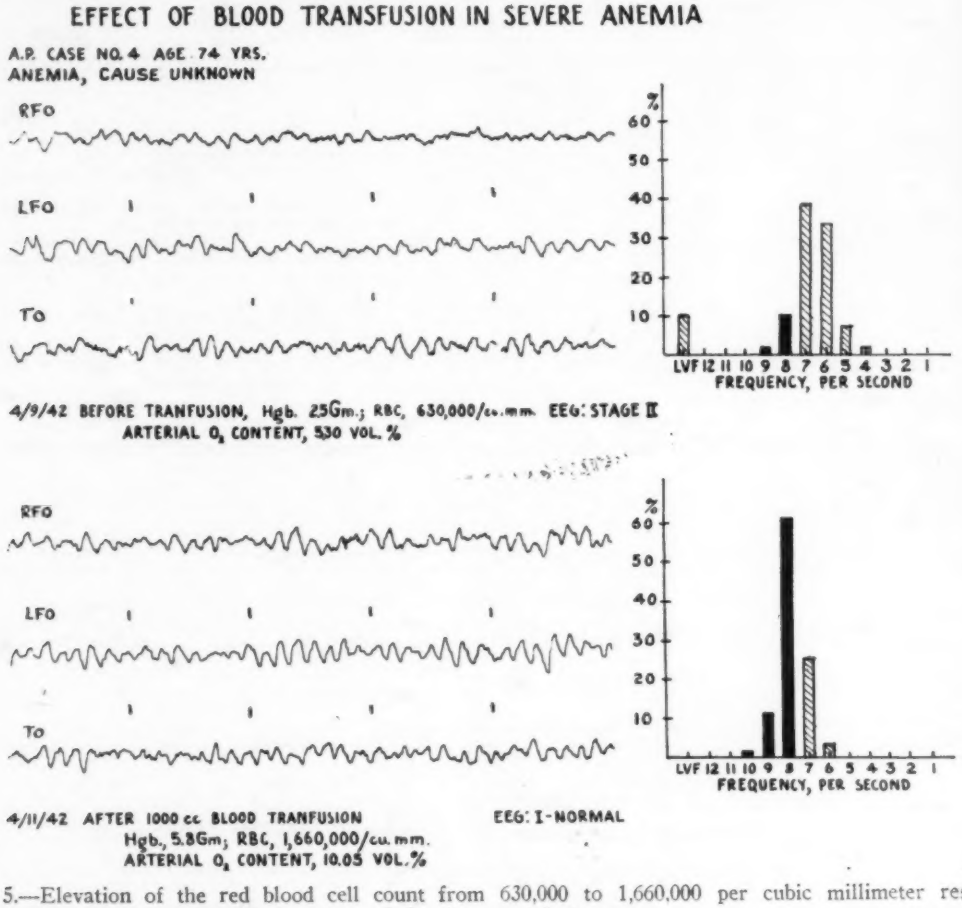

Fig. 5.—Elevation of the red blood cell count from 630,000 to 1,660,000 per cubic millimeter resulted in improvement in the electroencephalogram and in the mental status.

ADMINISTRATION OF ADRENAL CORTEX EXTRACT AND DEXTROSE TO PATIENTS WITH ADDISON'S DISEASE

Abnormal electroencephalograms have been reported for patients with Addison's disease in all stages of therapy.[4] Intensive observations on 2 patients afforded an opportunity to study the electrical activity of the brain during an addisonian crisis and during treatment with desoxy-

4. (*a*) Engel, G. L., and Margolin, S.: Neuropsychiatric Disturbances in Addison's Disease and Role of Impaired Carbohydrate Metabolism in the Production of Abnormal Cerebral Function, Arch. Neurol. & Psychiat. **45**:881 (May) 1941; (*b*) Neuropsychiatric Disturbances in Internal Disease: Metabolic Factors and Electroencephalographic Correlations, Arch. Int. Med. **70**:236 (Aug.) 1942. (*c*) Hoffman, W. C.; Lewis, R. A., and Thorn, G. W.: The Electroencephalogram in Addison's Disease, Bull. Johns Hopkins Hosp. **70**: 335, 1942.

TABLE 5.—*Effect on Electroencephalogram and Blood Sugars of Adrenal Cortex Extract in Cases of Addison's Disease*

Name; Sex; Age, Yr.	Case No.	Date	Treatment	Time	Electroencephalogram: Stage	Electroencephalogram: Percentage 8-12 per Sec. Frequency	Electroencephalogram: Dominant Frequency (per Sec.)	Intravenous Dextrose Tolerance Test, Mg./100 Cc.	Comment
E. Me. F 62	21	3/20	None	Fasting	II	19	6-8; LVF	99	Mild crisis; blood pressure 96/68; sodium 120 mEq./L.; chlorides 89 mEq./L.; hematocrit reading 48%
				½ hour	II	34	7-8	175	
		3/27	3/20-3/27: Total of 20 mg. of desoxycorticosterone acetate given intramuscularly. 3/20-3/26: 20 cc. of adrenal cortex extract q. i. d. 3/27: 20 cc. of extract given intramuscularly. 3/20-3/26: 15 Gm. sodium chloride q. i. d.	Fasting	Normal	66	8-9	100	Condition greatly improved Blood pressure 114/64; sodium 134 mEq./L.; chlorides 104 mEq./L.; hematocrit reading 32.7%
				End of infusion	Normal	81	8-9	309	
				1 hour	Normal	78	8-9	164	
				2 hours	Normal	88	8-9	127	
				3 hours	Normal	88	8-9	93	
				4 hours	Normal	71	8-9	95	
		4/7	3/27-4/7: 2-4.5 mg. of desoxycorticosterone acetate given intramuscularly q. i. d.; 5-15 Gm. sodium chloride q. i. d.	Fasting	I	37	7-8	103	Condition poorer; fever 99 to 104 F.; roentgenographic evidence of extension of pulmonary tuberculosis; blood pressure 150/100; sodium 140 mEq./L.; chlorides 111 mEq./L.; hematocrit reading 28%
				End of infusion	I	40	7-8	228	
				1 hour	I	25	7-8	134	
				2 hours	I	28	7-8	99	
				2½ hours	I-II	26	6-8	76	
				3 hours	I	35	7-8	80	
		4/13	4/8-4/11: 10 cc. adrenal cortex extract intramuscularly q. i. d.; 4/12: 20 cc.; 4/13: 38 cc. intramuscularly and intravenously; 9 Gm. sodium chloride q. i. d.	Fasting	I	40	7-8	93	Subjective improvement; temperature 99-100.2 F.; blood pressure 136/72; sodium 132 mEq./L.; chlorides 102 mEq./L.; hematocrit reading 28%
				End of infusion	I	47	7-8	295	
				1 hour	I	50	7-8	168	
				2 hours	I	49	7-8	115	
				3 hours	I	47	7-8	85	
				3½ hours	I	48	7-8	..	
R. W. M 59	22	10/10	None	Fasting	II	19	6-7	67	Mild crisis. Blood pressure 102/70; sodium 130 mEq./L.; hematocrit reading 47%
		10/15	One intramuscular injection of 10 mg. desoxycorticosterone acetate; 5 cc. adrenal cortex extract; 60 Gm. sodium chloride	Fasting	II	5	6-7	78	Moderate crisis. Blood pressure 85/50; sodium 130 mEq./L.
				½ hour (by mouth)	II	19	6-7	91	
		10/22	Daily administration of 3 mg. desoxycorticosterone acetate intramuscularly and 9 Gm. sodium chloride orally	Fasting	II-I	36	6-8	57	Improvement. Sodium 135 mEq./L.; hematocrit reading 46 %; blood pressure 126/88
				End of infusion	II-I	32	6-8	193	
				½ hour	II-I	33	6-8	124	
				1 hour	II-I	41	6-8	81	
				1½ hour	II-I	31	6-8	63	
				2 hours	..	..	...	55	
				2½ hours	II	24	6-7	51	Hypoglycemia reaction; moderate confusion
		10/28	Daily administration of 1.5-3 mg. desoxycorticosterone acetate intramuscularly and 6-9 Gm. sodium chloride orally	Fasting	I	57	7-8	55	Sodium 137 mEq./L.; blood pressure 114/74
		12/15	1 mg. desoxycorticosterone actate intramuscularly and 5 Gm. sodium chloride orally daily; thiamine hydrochloride, 60 mg. q. i. d.	Fasting	I	58	7-9	69	Blood pressure 100/85; condition good
				End of infusion	I	48	7-8	290	
				½ hour	..	..	...	130	
				1 hour	I-II	39	6-8	73	
				2 hours	I-II	36	6-8	65	
				2½ hours	II	22	5-7	57	Hypoglycemic reaction
		1/13	1 mg. of desoxycorticosterone acetate intramuscularly and 16 Gm. sodium chloride and 300 mg. nicotinamide orally daily	Fasting	I	56	7-8	81	Blood pressure 120/80; condition good
				End of infusion	I	48	7-8	229	
				1 hour	..	..	...	116	
				1½ hours	..	..	...	94	
				2 hours	I-II	34	6-8	77	
				2½ hours	I-II	35	6-8	61	Hypoglycemic reaction
				3 hours	..	..	...	51	
				10 min. after 10 Gm. dextrose	I	51	6-8	132	
		2/20	1 mg. of desoxycorticosterone acetate intramuscularly and 25 mg. calcium pantothenate and 6 Gm. sodium chloride orally daily	Fasting	I	60	7-9	74	Blood pressure 125/75; hematocrit reading 44%; condition good
				End of infusion	I	60	7-9	257	
				½ hour	..	..	...	148	
				1 hour	..	..	...	99	
				1½ hours	..	..	...	77	
				2 hours	I-II	46	6-8	60	
				2½ hours	I-II	38	6-8	47	Hypoglycemic reaction
				3 hours	II	18	5-7	50	
				10 min. after intravenous injection of dextrose	I	55	7-8	..	

TABLE 5.—*Effect of Electroencephalogram and Blood Sugars of Adrenal Cortex Extracts in Cases of Addison's Disease—Continued*

Name; Sex; Age, Yr.	Case No.	Date	Treatment	Time	Electroencephalogram: Stage	Electroencephalogram: Percentage 8-12 per Sec. Frequency	Electroencephalogram: Dominant Frequency (per Sec.)	Intravenous Dextrose Tolerance Test, Mg./100 Cc.	Comment
		3/31	1 mg. of desoxycorticosterone acetate intramuscularly and 6 Gm. sodium chloride and 12 mg. riboflavin orally daily	Fasting	I	66	7-9	73	Sodium 137 mEq./L.; chloride 110 mEq./L.; condition good
				End of infusion	I	52	7-8	210	
				1 hour	I	55	7-8	106	
				2 hours	..	..	...	63	
				2½ hours	I-II	37	6-8	60	Hypoglycemic reaction
				3 hours	II	32	5-8	53	
		4/4	15 cc. adrenal cortex extract intramuscularly daily for 4 days; 47.5 cc. adrenal cortex extract on fifth day	Fasting	I	61	7-8	81	Condition good
				End of infusion	I	61	7-8	224	
				1 hour	I	72	8-9	128	
				2 hours	I	58	7-8	106	
				2½ hours	I-0	81	8-9	75	
				3 hours	I-0	86	8-9	74	No hypoglycemic reaction
				3½ hours	I-0	90	8-10	74	
				1 hour (oral)	I	50	7-8	122	

corticosterone acetate and aqueous adrenal cortex extract, given separately and in combination. The electroencephalograms were generally obtained with the patient in the fasting state and during tolerance tests for dextrose given intravenously. The encephalographic data may be summarized as follows:

1. The electroencephalograms of both patients were most abnormal during the addisonian crisis, and with clinical improvement, regardless of the type of therapy used, the electroencephalogram improved (fig. 6).

2. Treatment with desoxycorticosterone acetate sufficient to produce an optimum clinical response resulted in improvement in the electroencephalogram but never in complete restoration to normal. One patient (R. W., case 22) was studied eight times during a six month period of treatment with desoxycorticosterone acetate and sodium chloride. The electroencephalogram showed maximum improvement in a few weeks and thereafter presented no essential change while the patient was receiving this form of treatment. It will be recalled that desoxycorticosterone acetate is effective in correcting the disturbances in electrolytic balance and in blood pressure but is without effect on carbohydrate metabolism. These results are in agreement with previous data.[4b,c]

3. The addition for a month at a time of individual members of the vitamin B complex group (thiamine, nicotinamide, riboflavin and calcium pantothenate) to the desoxycorticosterone acetate and sodium chloride therapy of patient R. W. (case 22) did not influence the electroencephalogram or the tolerance for dextrose. This is in accord with the data of Hoffman and associates.[4c]

4. Large quantities of aqueous adrenal cortex extract (Upjohn) [5] were most effective in producing improvement in the electroencephalogram. The patients were given 100 cc. of the extract in five to seven days (see table 5 for exact schedule).

In the case of E. Mc. (case 21), to whom a total of 20 mg. of desoxycorticosterone acetate was given in addition to the adrenal cortex extract, the electroencephalogram became entirely normal. During the next ten days the patient was treated with desoxycorticosterone alone. During this period, however, the temperature was elevated, and signs of activation of pulmonary tuberculosis appeared. The electroencephalogram became more abnormal. Treatment with 100 cc. of the adrenal cortex extract over five days now resulted in some improvement two to three hours after intravenous injection of dextrose but not during the fasting state.

R. W. (case 22) had been stabilized under treatment with desoxycorticosterone acetate and sodium chloride therapy for six months before a change to the adrenal cortex extract was made. After recovery from the initial crisis, the electroencephalographic and clinical states remained static for the entire period. The patient was given 107.5 cc. of the extract in five days (table 5), without any change in the electroencephalogram in the fasting state but with definite improvement after administration of dextrose.

5. Dextrose tolerance tests were carried out by intravenous administration of 0.5 Gm. of dextrose per kilogram of body weight in 10 per cent solution over the course of thirty minutes. Determinations of blood sugar were carried out at one-half and one hour intervals, as indicated.

During treatment with desoxycorticosterone, elevation of the levels of the blood sugar to between 193 and 290 mg. per hundred cubic centimeters did not influence the electroencephalogram. This is in contrast to the effect on normal records, in which there is a definite increase in

5. The Upjohn Company, Kalamazoo, Mich., supplied the adrenal cortex extract.

frequency during rising levels of the blood sugar.[6] During the period of decreasing blood sugar, however, the electroencephalogram showed slower and more abnormal activity.

R. W. (case 22) invariably displayed a hypoglycemic reaction with obvious confusion two and one-half hours after completion of the infusion (with the blood sugar at a level of from 47 to 61 mg. per hundred cubic centimeters). The electroencephalogram was most abnormal at this point but promptly improved when more dextrose was administered (fig. 7).

During treatment with adrenal cortex extract, the dextrose tolerance curves were higher, hypoglycemic reactions did not occur and the electroencephalogram either was unchanged or improved progressively during the period of falling levels of the blood sugar, in contrast to the results during treatment with desoxycorticosterone. The maximum improvement occurred three to three and one-half hours after the infusion of dextrose, or four to six hours after the last injection of extract, the time of maximum action (fig. 8).

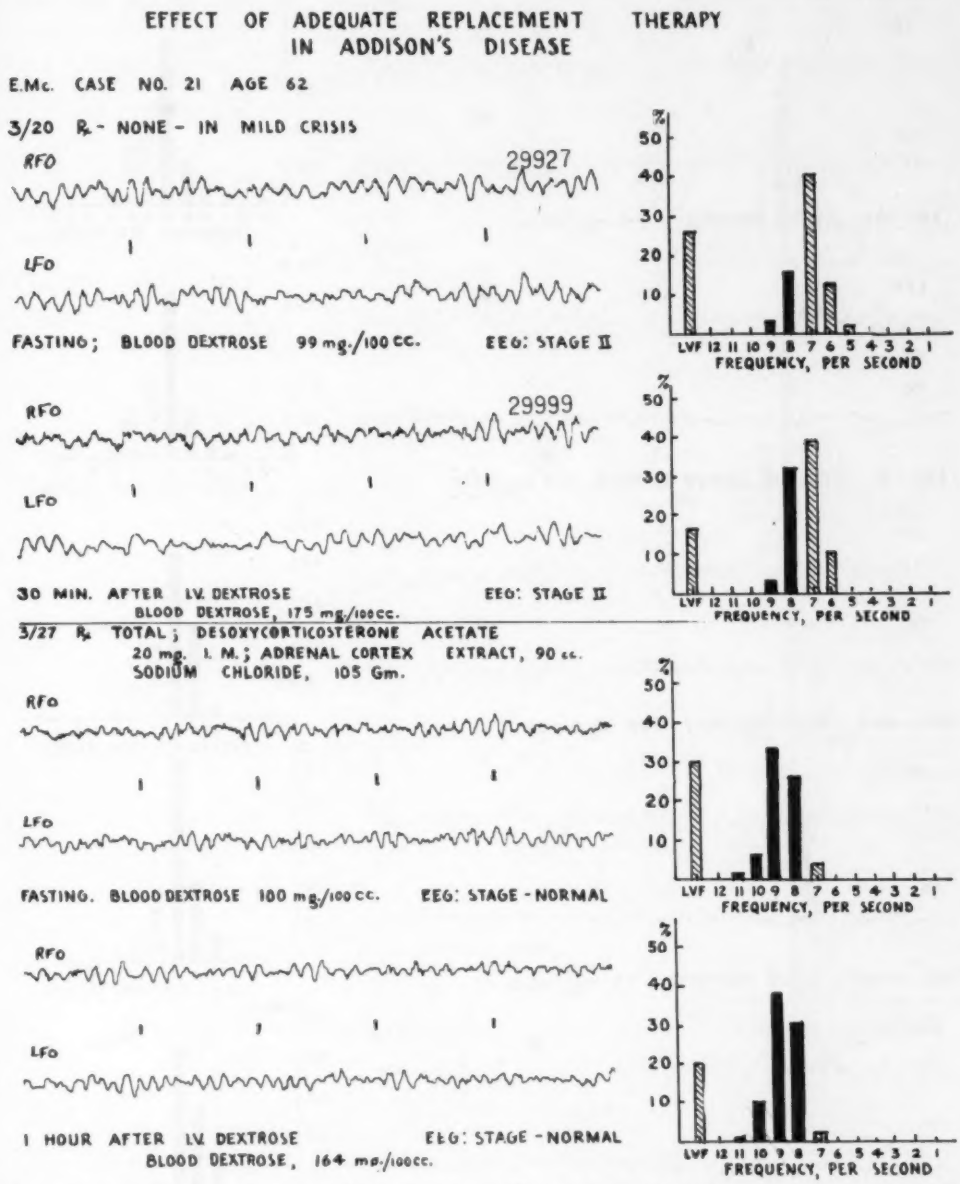

Fig. 6.—The electroencephalogram shifted from stage II to a normal pattern after one week of therapy with adrenal cortex extract, desoxycorticosterone acetate and sodium chloride. The mental status improved correspondingly.

6. Engel, G. L.; Romano, J.; Ferris, E. B., Jr.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on Effects of Physiologic Variations in Dextrose, Oxygen, Posture and Acid-Base Balance on the Normal Electroencephalogram, Arch. Neurol. & Psychiat. **51**:134 (Feb.) 1944.

Comment.—In previous reports one of us (G. L. E.) suggested that the electroencephalographic abnormalities associated with Addison's disease were related to the disturbance in carbohydrate metabolism, characteristic of Addison's disease.[4a, b] Thorn and associates,[4c] however, found no correlation with their patients between abnormal electroencephalograms and abnormal dextrose tolerance curves and were unable to detect any improvement in the electroencephalogram after therapy with aqueous adrenal cortex extract (4 to 8 cc. daily). In that study successive records were compared by gross inspection alone. The present data sug-

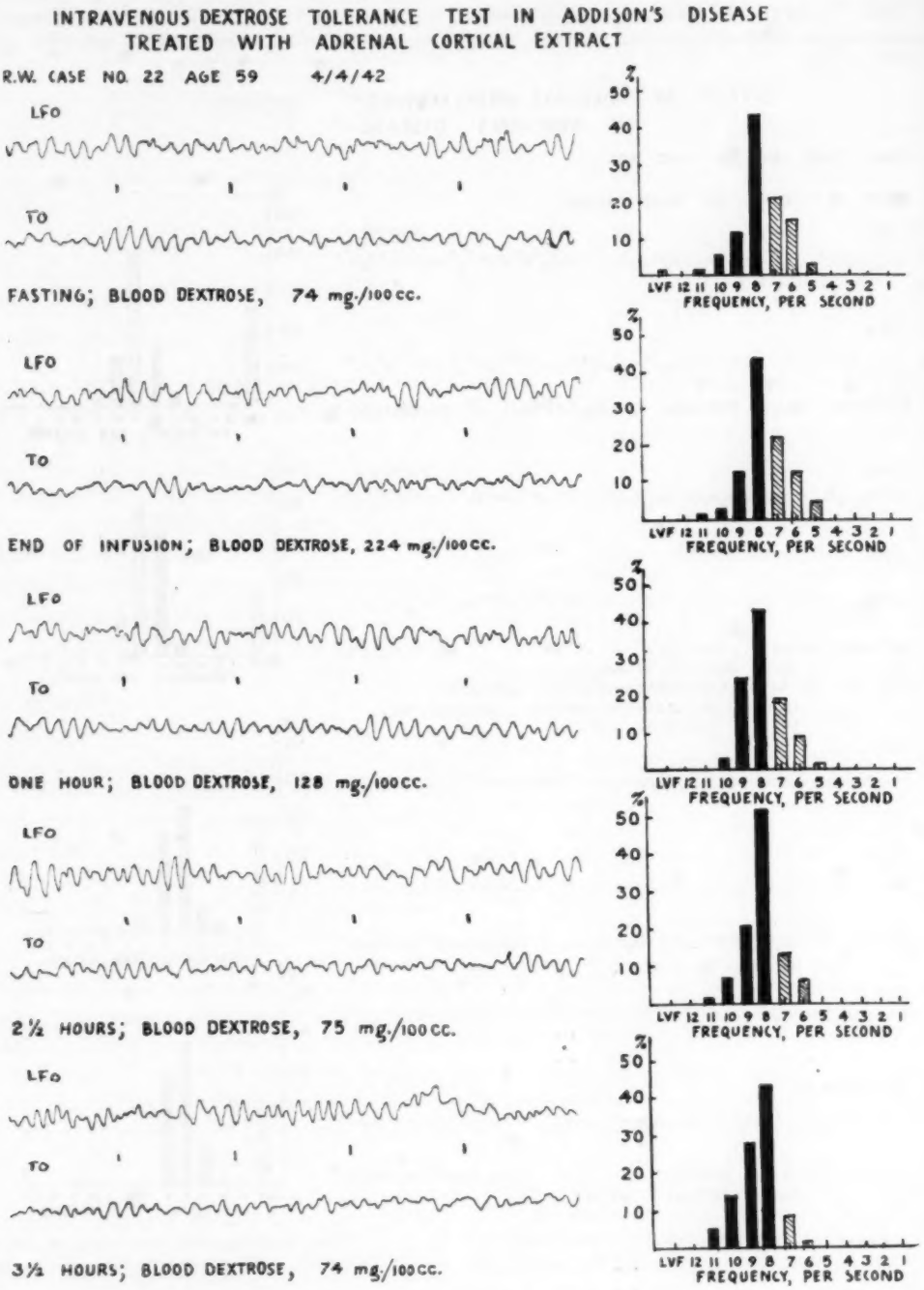

Fig. 7.—There was no improvement in the electroencephalogram with an increase in the blood sugar to 210 mg. per hundred cubic centimeters. At the end of two and a half hours the blood sugar fell to 60 mg. per hundred cubic centimeters, and the patient experienced a hypoglycemic reaction, marked by confusion and sweating. The electroencephalogram became more abnormal.

gest that a number of factors are involved. During the crisis disturbances in the level of awareness are common and are associated with electroencephalographic changes. However, with clinical and chemical recovery from crisis, the mental status returns to normal, while the electroencephalogram improves but does not necessarily become normal. Complete, or almost complete, return to normal of the electroencephalogram was attained only when a large amount of aqueous adrenal cortex extract or the extract plus dextrose was administered. Desoxycorti-

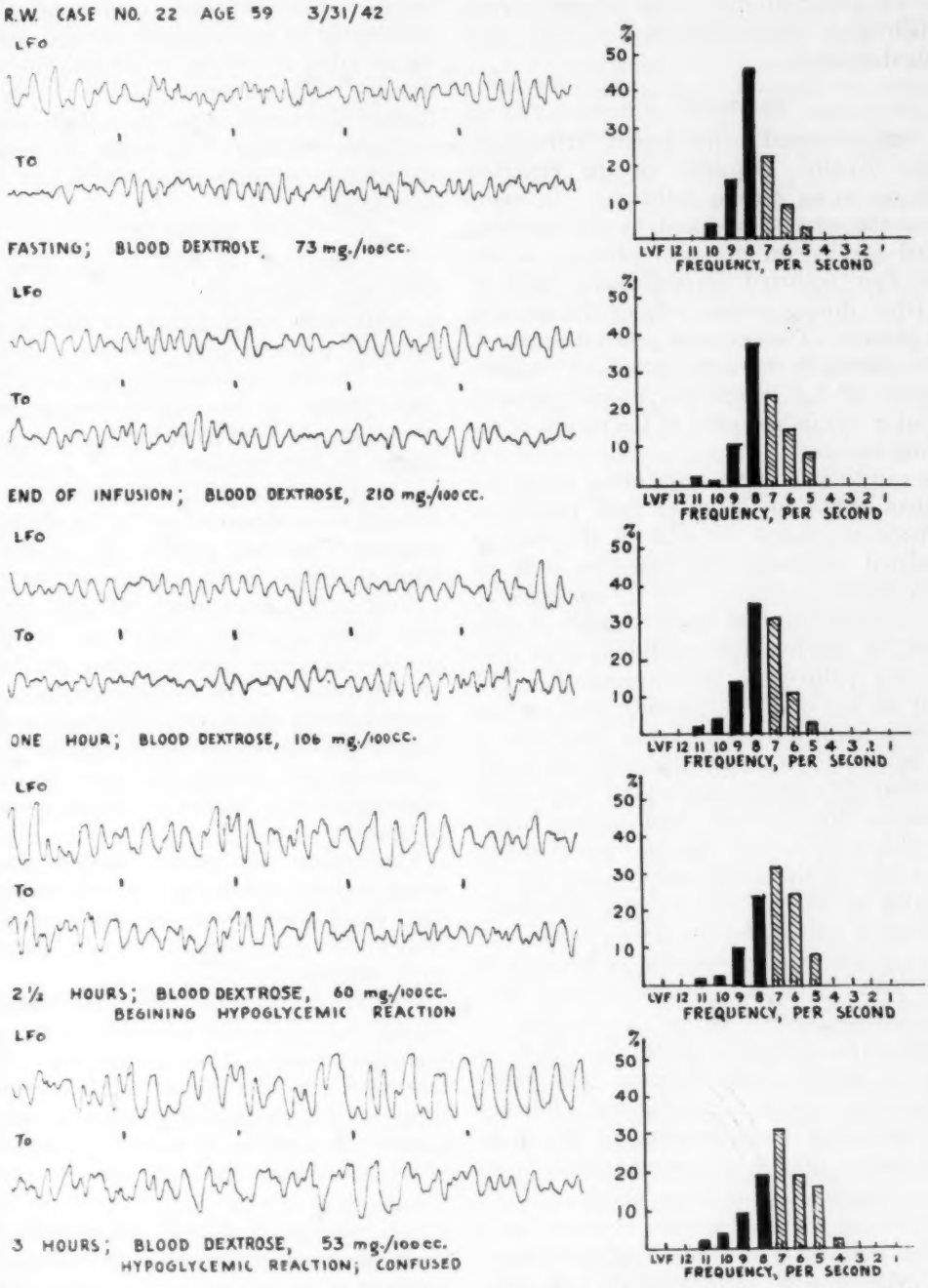

Fig. 8.—Electroencephalograms for the patient whose record appears in figure 7, after treatment with the extract for five days. There was no hypoglycemic reaction, and the electroencephalogram improved progressively in spite of falling levels of the blood sugar.

costerone, which has no effect on carbohydrate metabolism, alone or with dextrose, was ineffective. This, again, suggests, but does not prove, that at least in part the electrical abnormalities of the brain associated with Addison's disease are directly or indirectly related to disturbances in carbohydrate metabolism. The question of the relation of certain sterols of the adrenal cortex to carbohydrate metabolism of the brain warrants further study.

COMMENT

The data presented in this report further confirm the dynamic character of the electrical changes occurring during delirium.[1] In many instances the effects produced by the methods described yielded an accurate preview of the changes that occurred spontaneously days or weeks later, during recovery from the primary disease process. The response, when it occurred, followed essentially the same pattern of progressive stages as that which was noted spontaneously, but it was independent of the nature of the provoking factors.

Little can be said at this time about either the mechanism or the specificity of these responses. The choice of clinical material in the various experimental categories was based on well established clinical practices. We do not know as yet, for example, whether administration of oxygen would be effective with conditions other than cardiac and pulmonary decompensation. The fact that all but 1 of the patients with cardiac decompensation had normal oxygen saturation of arterial blood and yet many responded well to administration of oxygen makes it clear that simple anoxemia is not the sole determining factor. Recent studies on normal subjects [6] have demonstrated a shift in alpha frequency during the administration of 100 per cent oxygen. Similarly, while we have demonstrated a return toward the normal response to administration of dextrose in patients with Addison's disease treated with aqueous adrenal cortex extract in contrast to the desoxycorticosterone is given, the effects of dextrose in patients with delirium from other causes have not yet been investigated. Further studies, including measurements of the total cerebral oxygen uptake, are contemplated in an attempt to clarify some of these problems.

Regardless of the mechanisms, however, it is clear from these data that the intelligent treatment of delirium must include efforts to reverse the major physiologic derangements accompanying the underlying disease. The statement that permanent cortical damage becomes increasingly likely the longer the noxious factors are active is amply supported by clinical and electroencephalographic observation. The greatest range of reversibility is found in the early and acute phases. The delirious cardiac patient with pulmonary disease should not be permitted to remain anoxemic until spontaneous recovery occurs. Cheyne-Stokes respiration should be terminated by any available method, such as administration of oxygen or theophylline ethylenediamine. Special attention should be directed toward restoration of the normal physiologic and biochemical milieu of the brain and avoidance of the addition of further noxious factors, e. g., certain drugs.

SUMMARY

One hundred per cent oxygen was administered in a total of 20 experiments to 9 delirious patients with congestive heart failure and to 4 delirious patients with pulmonary decompensation. The electroencephalogram showed definite improvement in 10 experiments, probable improvement in 7 experiments and no significant change in 3 experiments.

Three patients with congestive heart failure showed more abnormalities in the electroencephalogram when they were in the recumbent than when they were in the sitting position.

Four of 6 patients with Cheyne-Stokes respiration showed phasic variations in the electroencephalogram corresponding to the phases of respiration. The electroencephalogram improved during the hyperpneic phase and showed more abnormalities during the apneic phase. For 2 patients with pronounced stage IV electroencephalograms no significant changes were demonstrable.

One patient with extreme anemia of unknown cause had a more normal electroencephalogram after blood transfusion. The hemoglobin concentration rose from 2.5 to 5.8 Gm. per hundred cubic centimeters.

Two patients with Addison's disease were studied during therapy with desoxycorticosterone acetate and adrenal cortex extract. Adequate treatment with the former resulted in improvement in the electroencephalogram, but not in complete restoration to normal. Large amounts of adrenal cortical extract, sufficient to produce a significant change in the dextrose tolerance curve, resulted in further improvement in the electroencephalogram, particularly during administration of dextrose.

In the treatment of delirium correction of reversible physiologic disturbances is important.

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BIOCHEMICAL ASPECTS OF GLUTAMIC ACID THERAPY FOR EPILEPSY

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Recently, the use of *dl*-glutamic acid hydrochloride in the treatment of epileptic patients suffering from seizures of the petit mal and the psychomotor type was described.[1] Administration of the racemic amino acid hydrochloride to patients who were resistant to the usual anticonvulsant therapy resulted in a decrease in the frequency of seizures and in an increase in mental and physical alertness. The anticonvulsant therapy, though ineffective previously, was continued through the period of administration of the amino acid hydrochloride. Seizures of the grand mal type were unaffected, or were increased, by this treatment.

It is of primary interest to discover the mechanism through which *dl*-glutamic acid hydrochloride exercises its effect, and the experiments described in this paper were directed toward this objective.

As was pointed out previously,[1] the use of the *dl*-glutamic acid hydrochloride was suggested (*a*) by the close relation of the natural, *l* (+) isomer to cerebral metabolism and (*b*) by the mildly acidifying effect which the racemic amino acid hydrochloride would be expected to have.

Studies on the influence of the administration of *dl*-glutamic acid hydrochloride on the acid-base balance of the blood and urine and the fate of this substance in the human subject and on the effect of administration of the *l* (+) isomer indicate that the therapeutic results may be ascribed in large part to the *l* (+)-glutamic acid, and not to the acidifying effect of the racemic amino acid hydrochloride.

EXPERIMENTAL DETERMINATION OF ACID-BASE BALANCE

The subjects of the investigation were patients with seizures of the petit mal or psychomotor type. The beneficial effect of the administration of *dl*-glutamic acid hydrochloride on 3 of the patients (S. K., R. J. and M. B. S.) was described previously.[1] It was impossible to hospitalize the patients throughout the investigation, but at approximately three week intervals they stayed in the hospital for a three day period, during which samples of the blood and urine were collected under controlled conditions. On the morning of the third day a sample of blood was withdrawn before breakfast, and the cell volume, the carbon dioxide content and the chloride concentration of the serum were determined by standard laboratory procedures.[2] The urine of the twenty-four hours preceding the taking of the sample of blood was collected under toluene, and the p_H (glass electrode method) and the values for ammonia, titrable acid,[2] and total base [3] were determined. The first three sets of data, obtained during the first six weeks, served as controls. On the day following the third collection of blood and urine, the administration of *dl*-glutamic acid hydrochloride was begun.

Since the results were similar for all the patients studied, the data for only 1 of them are given in the accompanying table. The carbon dioxide content and the chloride concentration of the serum during the administration of the racemic amino acid hydrochloride did not vary significantly from the control values, which were found to agree in magnitude and variation with those for healthy human subjects, as determined by Shock and Hastings.[4] Of the patients who received daily 2.4 to 3.6 Gm. of hydrochloric acid as glutamic acid hydrochloride, the chloride concentration in the serum of only 1 (M. S. B.) appeared to have increased slightly (from 102 to 108 millimols). No significant shift occurred in the acid-base balance even after prolonged intake of glutamic acid hydrochloride.

Since the sample of blood was taken at least fourteen hours after the last intake of *dl*-glutamic acid hydrochloride, these conclusions apply only to permanent changes in the acid-base balance of the blood. No study of the immediate effect of the intake of the *dl*-amino acid hydrochloride was undertaken.

The urine of the patients after administration of *dl*-glutamic acid hydrochloride presented the

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1. Price, J. C.; Waelsch, H., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122**:1153 (Aug. 21) 1943.

2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932.

3. Consolazio, W. V., and Talbott, J. H.: J. Biol. Chem. **132**:753, 1940.

4. Shock, N. W., and Hastings, A. B.: J. Biol. Chem. **104**:585, 1934.

picture of the effect of a mild acidifying agent. The p_H was lowered to from 5 or 6, and the excretion of ammonia, fixed base and titrable acid was increased. In 3 of 4 patients a definite, but temporary, diuretic effect of the amino acid hydrochloride was evident.

From the seventy-two hour specimen of urine of 3 of the patients, the isolation of *d* (—)-glutamic acid was undertaken. Since, according to Ratner,[5] the unnatural isomer of glutamic acid is excreted in rats as pyrrolidincarboxylic acid, the urines were brought to a concentration of twice normal hydrochloric acid and hydrolyzed for sixteen hours on the steam bath. Customarily the isolation of glutamic acid from urine is carried out by means of the Neuberg precipitation method, with successive precipitations of the barium or the calcium salt. In order to save the mercury salt, the first step was eliminated and the glutamic acid precipitated directly from the hydrolyzed and concentrated urine by addition of barium hydroxide and 5 volumes of alcohol.

From each of the urines the unnatural, *d* (—), glutamic acid was isolated in pure form in small yield. On the basis of the daily intake of the racemic acid, 20 per cent of the unnatural isomer was isolated from the urine of patient S. K., 15 per cent from the urine of patient M. B. S. and 7 per cent from the urine of patient J. R.

EFFECT OF ADMINISTRATION OF *l* (+)-GLUTAMIC ACID

When *l* (+)-glutamic acid was administered to about 20 patients who had experienced recurrent petit mal seizures, both the frequency and the severity of the attacks were reduced. Attacks of grand mal were essentially unchanged or were increased in frequency. The effect on psychomotor seizures was less easy to demonstrate but was often commented on by the patient and his relatives.

The following 2 cases are illustrative of the results obtained in treatment of classic petit mal epilepsy.

CASE 1.—Repeated neurologic and physical examinations of the patient, a 12 year old boy, revealed nothing abnormal. Petit mal seizures, which had occurred at a frequency of from twenty-five to fifty or more a day for four years, were unaffected by diphenylhydantoin sodium–phenobarbital therapy. A six months' trial with the ketogenic diet resulted in moderate reduction in the number of seizures, but the patient refused to continue under the rigid regimen. Administration of *dl*-glutamic acid hydrochloride, in daily doses of 12 Gm., resulted in reduction in the number of seizures to from five to twenty-five a day. The parents, school instructors and friends reported spontaneously that the patient was more congenial, cooperative and affable. Peculiar egocentric attitudes were decreased. Concentration and application in his school work were improved.

The seizures recurred at their former frequency after the administration of *dl*-glutamic acid hydrochloride was discontinued. Use of ammonium chloride, 4 Gm. a day, failed to alter the frequency or character of the seizures.

Acid-Base Balance of Blood and Urine of Patient R. J.

Date, 1943	Hematocrit Reading	Carbon Dioxide, mEq. per Liter	Serum Chloride, mEq. per Liter	Volume, Liters	p_H	Urine (24 Hours) Titrable Acid, mEq.	Ammonia, m.Eq	Total Base, mEq.	Comment
1/12	48	28.9	96	2.7	7.0	13.5	25.0	535	
1/26	..	31.3	97	2.6	6.6	23.7	19.0	418	
2/10	44	32.1	100	1.6	6.3	28.2	42.0	342	
2/23	50	32.8	95	2.0	5.8	35.4	83.0	480	12 Gm. *dl*-glutamic acid hydrochloride
3/ 9	..	30.5	96	4.0	5.8	52.0	110.0	580	
3/23	44	29.2	97	3.4	5.0	60.0	134.0	640	
4/ 6	44	30.0	100	2.4	5.7	36.0	84.0	450	
4/20	..	....	...	2.8	5.6	44.0	81.0	360	
5/11	42	28.6	97	2.0	6.4	22.0	71.0	572	16 Gm. *dl*-glutamic acid hydrochloride
6/ 8	46	31.0	95	2.6	6.0	33.0	73.0	456	
7/22	42	29.4	102	1.0	5.3	52.0	76.0	...	

Carbaminoylcholine chloride, 26 mg. in divided doses, combined with diphenylhydantoin sodium, 0.3 Gm., failed to reduce materially the frequency of the attacks. The number of days during which only twenty-five attacks occurred increased, with a relative decrease in the number of days on which fifty attacks were noted.

Carbaminoylcholine-diphenylhydantoin therapy was replaced by administration of *l* (+)-glutamic acid. A larger quantity than 8 to 12 Gm. was not required to obtain a favorable result. A further reduction of the frequency of the attacks over that observed with *dl*-glutamic acid hydrochloride was noted. The patient's parents and school instructors reported that there were days during which no seizures were observed, and the patient stated that he was not aware of momentary interruptions of consciousness on these days.

Improvement in personality was similar to, and qualitatively identical with, the changes noted during administration of *dl*-glutamic acid hydrochloride.

In this case, there is little doubt that the improvement, both in the frequency of seizures and in emotional stability, was related to administration of *l* (+)-glutamic acid alone. Diphenylhydantoin sodium, diphenylhydantoin-phenobarbital therapy, a ketogenic diet, ammonium chloride and carbaminoylcholine-diphenylhydantoin ther-

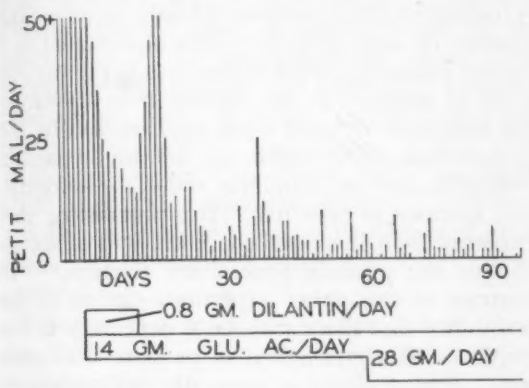
5. Ratner, S.: J. Biol. Chem. **152**:559, 1944.

apy had neither reduced the frequency of attacks nor improved the personality of the patient.

CASE 2.—A man aged 23 was in good health until ten years ago, when he became aware of short lapses of consciousness. His parents and friends recalled periods during which he failed to answer questions, ceased talking and apparently stared into space. The attacks recurred at the rate of five to fifty per day.

The first of a series of eight grand mal attacks occurred six years ago. Repeated physical and neurologic examinations revealed nothing significant. A roentgenogram of the skull, a pneumoencephalogram, a complete blood count, the results of urinalysis and the basal metabolic rate were normal. Values for the blood sugar had been noted by previous observers to range from 46 to 98 mg. per hundred cubic centimeters, both in the fasting state and as single estimations obtained during a dextrose tolerance test. Dextrose, dextrose-insulin and insulin tolerance curves were within normal limits.

Phenobarbital, diphenylhydantoin sodium and bromides, either alone or in combination, were ineffective in reducing the attacks. The ketogenic diet was poorly tolerated by the patient. Ammonium chloride failed to ameliorate the symptoms.



Effect of administration of *l*(+)-glutamic acid in varying doses, with and without diphenylhydantoin sodium, on the frequency of petit mal seizures.

The attacks were notably reduced during a fasting period of thirty-six hours. They increased during administration of a diet containing 300 Gm. of carbohydrate daily. Administration of diphenylhydantoin sodium (0.4 Gm.) was continued throughout the tests, as in the control period.

Administration of *l*-glutamic acid in doses of 14 to 28 Gm. daily, with or without diphenylhydantoin sodium, was associated with a reduction in the frequency of attacks which was roughly proportional to the dose. The occurrence of seizures varied from none up to ten daily, and their severity was decreased. In this case, *l* (+)-glutamic acid was decidedly more effective than the other measures tried. The morale of the patient was improved; however, there was no evidence of any effect on the personality or the emotional stability. The p_H of the urine (glass electrode method) fluctuated within a range of 6 to 7.5, with occasional lowering to 5.5.

COMMENT

In the beginning of our study, *dl*-glutamic acid hydrochloride and *l* (+)-glutamic acid were given only in combination with anticonvulsant drugs, despite the fact that the drug therapy had proved ineffective for the patients concerned. Later, the glutamic acid preparations were given patients without an accompanying drug, as in the 2 cases described in this paper. The results presented here indicate that the effect observed was due to the administration of the natural, *l* (+) isomer. No shift in the acid-base balance of the blood following the administration of *dl*-glutamic acid hydrochloride could be detected with the methods applied, and the decrease in seizures occurred too soon for it to appear likely that this was the effect of a mildly acidifying agent. The administration of the acidifying substance expressed itself in lowering of the p_H of the urine, in an increased excretion of ammonia and in a slight increase of the excretion of total base and of titrable acidity.

Whereas the lack of an acidifying effect on the blood of the racemic acid hydrochloride does not exclude the possibility that some other property of the racemate might be responsible for the therapeutic effect observed, the clinical observations after the administration of the *l* (+) isomer make it probable that this compound is the effective component of *dl*-glutamic acid hydrochloride. The fact that a naturally occurring, nonessential amino acid, which is a major component of the food and body proteins, has a distinct action, otherwise encountered only with essential food components, is of particular biochemical interest. A daily protein intake of 70 Gm. would correspond approximately to an intake of natural glutamic acid of 7 to 10 Gm. The proteins of the body itself contain between 10 and 20 per cent of glutamic acid. It is remarkable, therefore, that as little as 4.8 Gm. of *l* (+)-glutamic acid administered in 12 Gm. of the racemic hydrochloride should have the therapeutic effect observed. Furthermore, glutamic acid occupies a central position in the metabolic processes involving transamination and carbohydrate cycles, a fact indicating the rapid metabolic transformation this amino acid undergoes in the body.

From our results, it appears that in spite of the abundant occurrence of a particular compound in the food and body and the ease with which it can be synthesized in the body, relatively small amounts of it, administered in addition to a balanced diet, may have beneficial effects under certain conditions. It is indubitably too early to interpret our results in terms of a possible deficiency which is overcome by the administration of glutamic acid. Nothing is known about the specificity of the observed action. There might well be other nitrogenous, or nonnitrogenous, body constituents which have the same effect as that observed with glutamic acid.

Furthermore, the substance may act indirectly by influencing organs other than the nervous tissue or by modifying the absorptive process in the intestine of substances, such as minerals.[6]

In consequence of the results obtained with glutamic acid in treatment of patients with petit mal, two studies were carried out which may have a bearing on the understanding of the mechanism involved. Zimmerman and Ross[7] investigated the effect of *l* (+)-glutamic acid and *dl*-pyrrolidincarboxylic acid on the maze-learning ability of rats, as measured by the number of trials and errors and the time required by the animals to run the maze. Rats which received glutamic acid or its derivative showed significantly greater learning ability than the controls, which were fed the complete balanced diet without the amino acid supplement. The addition of aminoacetic acid to the diet had no effect. The results of these experiments, which were suggested by observations on the mental behavior of patients receiving glutamic acid, give further indication that glutamic acid appears to influence cortical activity by direct or indirect means. Furthermore, the comparison with aminoacetic acid shows that this is not a property peculiar to all amino acids.

Recently, Nachmansohn, John and Waelsch[8] showed that glutamic acid has an adjuvant action on the enzyme system which synthesizes acetylcholine from choline and acetic acid.[9] After the enzyme extract was dialyzed, the decreased synthesizing power of the system could be restored partially by addition of glutamic acid (or citric acid) to the extract. These observations, which point to specific involvement of glutamic acid in biochemical mechanisms intimately connected with the function of nervous tissue, may become of increased importance if there should be found a deficiency of glutamic acid or substances metabolically related to it in patients with petit mal.[10]

At this point in the study it is not possible to obtain a common denominator for the effect observed with glutamic acid and that observed with other substances used in treatment of patients subject to attacks of petit mal. The outstanding therapeutic measure, namely, the ketogenic diet, produces not only an increased concentration of ketone bodies, but acidosis. The doubtful results obtained with ammonium chloride and the probable exclusion of an acidotic effect of glutamic acid therapy suggest the possibility that the acidosis accompanying the use of the ketogenic diet may not be directly responsible for the effects observed. It is possible that the production of acetoacetic acid influences the acetylation of choline to acetylcholine.

It is of major interest in this connection that glutamic acid is effective only in treatment of patients with petit mal. In patients suffering from attacks of grand mal glutamic acid not only is ineffective but sometimes actually increases the number of such seizures. This observation is a further indication of the differences in the various types of epilepsy, as has already been shown by the difference in brain wave patterns and by the preferential effectiveness of diphenylhydantoin sodium in cases of grand mal and of the ketogenic diet in cases of petit mal. It is interesting that experimentally increased concentrations of acetylcholine can produce generalized seizures.[11] In contrast to this, other experiments point to the possibility that there may be a deficiency in the synthesis of acetylcholine in patients with petit mal. A final decision as to the mechanism involved in the action of glutamic acid, however, must be left to future experiments.

SUMMARY

The administration of *dl*-glutamic acid hydrochloride in amounts which benefit patients suffering from attacks of petit mal does not result in a significant shift of the acid-base balance of the blood. Urinalysis showed the effect of a mildly acidifying agent; *d* (—)-glutamic acid was isolated from the urine of the patients.

Administration of *l* (+)-glutamic acid is as effective as that of *dl*-glutamic acid hydrochloride. These results suggest that the therapeutic effects may be ascribed to the *l* (+)-glutamic acid.

Mrs. R. Howard-Bower, of the Department of Biochemistry, made the analyses of the blood, and Mrs. B. Prescott assisted in the work.

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Neurological Institute of New York.

6. McCance, R. A.; Widdowson, E. M., and Lehmann, H.: Biochem. J. **36**:686, 1942.

7. Zimmerman, F. T., and Ross, S.: To be published.

8. Nachmansohn, D.; John, H. M., and Waelsch, H.: J. Biol. Chem. **150**:485, 1943.

9. Nachmansohn, D., and Machado, A. L.: J. Neurophysiol. **6**:397, 1943.

10. Krebs (Biochem. J. **29**:1951, 1935) found that brain tissue contains an enzyme which synthesizes glutamine from *l* (+)-glutamic acid and NH_4^+, a reaction which is inhibited by the presence of the unnatural isomer of glutamic acid. It has been reported recently (Sapirstein, M. R.: Proc. Soc. Exper. Biol. & Med. **52**:334, 1943) that generalized seizures in rabbits produced by intravenous administration of an ammonium salt may be suppressed by a preceding intravenous injection of *l* (+)-glutamic acid.

11. Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of Cortex, Arch. Neurol. & Psychiat. **48**:382 (Sept.) 1942.

FATALITIES ASSOCIATED WITH ELECTRIC SHOCK TREATMENT OF PSYCHOSES

REPORT OF TWO CASES, WITH AUTOPSY OBSERVATIONS IN ONE OF THEM

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A small number of deaths due to electric shock have been reported in the literature since the introduction of electrotherapy. Kolb and Vogel [1] estimated a death rate of 0.05 per cent in 7,207 cases, and Impastato and Almansi,[2] a mortality rate of 0.8 per cent in 11,000 cases. As a rule, death is due to a defect in some organ other than the brain—usually the heart—which is aggravated by the convulsive treatment. However, some deaths are completely unexplainable. Impastato and Almansi,[2] Ziegler [3] and Ebaugh and his associates [4] reported cases in which failure of the heart played the deciding role. Cash and Hoekstra [5] and Ebaugh and associates [4] recorded fatalities in cases in which curare was given before the electric convulsion. Cash and Hoekstra [5] stated that death came suddenly, about two hours after the treatment, and was probably of cardiac origin. Ebaugh and associates [4] stated that immediate pulmonary arrest caused death.

Ebaugh and associates [4] tabulated in some detail the data in 9 cases which had been reported in the literature up to July 1942. The ages in 7 of these cases ranged from 50 to 79; in 1 case the patient was 45 and in 1 29 years of age. In 3 cases death occurred one to four months after the treatment, and in the other 6 cases, anywhere from immediately to three days after a treatment. The latter cases are the significant ones because the time of death followed so closely the induced convulsion. In 4 of these 6 cases death followed the treatment immediately and was due to cardiac or respiratory failure; in 1 case coronary thrombosis caused the patient's death one hour and thirty-five minutes after the treatment, and in 1 case the patient died in status epilepticus three days after the treatment. In 4 of these 6 cases, again, one to three treatments were given; in 1 case, nineteen treatments, and in 1 case, thirteen treatments. In 3 cases autopsy was performed; in 1 of these the patient, aged 75, had advanced changes associated with arteriosclerosis, and the brains in the other 2 cases, in each of which the patient was 57 years of age, showed several small areas of cortical devastation, diffuse degeneration of nerve cells in the cortex, small areas of recent necrosis and astrocytic proliferation. These last 2 cases were reported by Ebaugh and his co-workers.

The following 2 cases are reported here for their interest and because they add material for future study in a still obscure field.

REPORT OF CASES

CASE 1.—*Family and Past History.*—M. B. was born Nov. 15, 1898. She had no unusual diseases in childhood and graduated from grammar school at the age of 14. She worked regularly from this time except for a few weeks in her twenty-eighth year, when she was confined to a convalescent home because she was "run down from overwork." She married at the age of 37 and had an abortion one year later. She was of Protestant faith, went to church regularly and was moderate in her habits. She was described as worrisome and conscientious in her work. The family history was negative for nervous and mental disease.

Psychosis.—The first change in her behavior was noted in the early part of February 1941, when she showed an abnormal interest in Christian Science. Shortly thereafter, she began to think that she had cancer and went to several physicians, who could not dissuade her from the idea. She became depressed and self condemnatory and expressed the opinion that her mind was "slipping." She continued to work, nevertheless, until one week before her admission to the hospital, on July 3, 1941. She finally became so agitated that the family could not manage her, and the physician advised hospitalization.

On admission there was accentuation of her leading symptoms. The agitation and depression increased;

1. Kolb, L., and Vogel, V.: The Use of Shock Therapy in Three Hundred and Five Mental Hospitals, Am. J. Psychiat. **99**:90-100 (July) 1942.

2. Impastato, D., and Almansi, R.: A Study of Over Two Thousand Cases of Electrofit-Treated Patients, New York State J. Med. **43**:2057-2064 (Nov. 1) 1943; Electrically Induced Convulsions in Treatment of Functional Mental Disease, M. Ann. District of Columbia **10**:163-170 (May) 1941.

3. Ziegler, L., in discussion on Evans, V.: Physical Risks in Convulsive Shock Therapy, Arch. Neurol. & Psychiat. **48**:1017-1020 (Dec.) 1942.

4. Ebaugh, F.; Barnacle, C., and Neubuerger, K.: Fatalities Following Electric Convulsive Therapy, Arch. Neurol. & Psychiat. **49**:107-117 (Jan.) 1943.

5. Cash, P., and Hoekstra, C.: Preliminary Curarization in Electric Convulsive Shock Therapy, Psychiatric Quart. **17**:20-34, 1943.

ideas of sinfulness multiplied, and self condemnation became more persistent. At times she moaned all day and was either very restless or mute and motionless. Physical examination revealed nothing significant. The diagnosis of involutional melancholia was established.

Two months after her admission her condition became somewhat worse. After a wet pack her temperature rose to 106.4 F., but she had no physical complaints. Rales were discovered at the base of the right lung, and, although a roentgenogram of the chest revealed nothing significant, a diagnosis of bronchopneumonia was made. The temperature rapidly returned to normal. During November 1941, for the first time, her symptoms became less severe. She was then transferred to a ward for the chronically ill, where she had several exacerbations of the psychosis; she admitted having auditory hallucinations of a derogatory nature and made several suicidal attempts.

Electric Shock Treatment.—On July 6, 1942 electric shock therapy was begun. She was given three treatments a week and by August 5 had had one petit mal and thirteen grand mal convulsions. The dose ranged from 110 to 140 volts, applied for two-tenths second. The convulsion and the postconvulsive state were of the usual character. After a few treatments she showed signs of improvement, which progressed until finally she was free of delusions and hallucinatory experiences. She was no longer depressed and self condemnatory and took an interest in herself and her surroundings. Treatment was finally stopped because she became slightly elated and confused after the twelfth treatment. Although she was informed that she would be released after a short rest, she kept insisting that she be sent home immediately because she felt well and wanted to attend her niece's wedding. She became moderately restless, but transfer to a ward for disturbed patients was not necessary until 1 a. m. of August 11. At this time she became acutely disturbed, screamed and assaulted people about her. It was necessary to place her in restraint, and during that day she received ¼ grain (15 mg.) of morphine sulfate and 1/100 grain (0.6 mg.) of scopolamine hydrobromide at 10 a. m., 2 p. m. and 9 p. m. However, she slept little and struggled against her restraints most of the time. She refused to eat and had to be fed with a tube. At 7:30 a. m. of August 12 her temperature was 108 F. plus; her skin was dry, and her tongue was parched. She was extremely restless, kept screaming unintelligible words and seemed to be using her last ounce of energy. At this time she received 1.5 cc. of a 25 per cent solution of nikethamide (pyridine betacarboxylic acid diethylamide) intramuscularly and 50 cc. of a 50 per cent solution of dextrose intravenously. She was packed in ice, and administration of 5 per cent dextrose isotonic solution of sodium chloride by clysis was begun. At 8:30 a. m. 5 grains (0.3 Gm.) of barbital sodium and 3.5 grains (0.2 Gm.) of sodium amytal were administered intramuscularly, in an attempt to quiet her. Her temperature fell to 104.4 F. by 9:15 a. m. but rose to 106.4 F. one hour later. By this time she exhibited convulsive movements involving her whole body and sometimes resembling status epilepticus. She was, therefore, given 3 grains (0.19 Gm.) of sodium amytal intravenously. This stopped the convulsive movements. However, her pulse soon became so weak and her general depression so profound that it was feared she was about to die. The corneal reflexes were absent and the pupillary reflexes poor. She was then given 1 cc. of epinephrine hydrochloride (1:1,000) intramuscularly and 1.5 cc. of a 25 per cent solution of nikethamide intracardially. Her pulse could not be obtained, but she continued to breathe regularly and rapidly. All this time she was absorbing the hypodermoclysis well. At 11 a. m. her temperature was 100.2 F., and the ice was removed from her body. She became a little restless and moaned unintelligibly, but could not speak. At 12:50 p. m. she was given 1.5 cc. of a 25 per cent solution of nikethamide because her pulse was imperceptible. She responded to the pain of the injection by thrashing about. At 2 p. m. her temperature was 100 F. At 3:10 p. m. another 1.5 cc. of the solution of nikethamide was given intramuscularly to maintain her cardiovascular system. At 3:30 p. m. it was noted that she was absorbing the clysis rather poorly, and at 4 p. m. her temperature was up to 102 F. Her lungs were clear except for occasional moist rales. Her temperature slowly rose; respirations became more shallow and rapid, and her pulse became imperceptible. At 7 p. m. her temperature was 106.2 F. and her respirations 52 a minute. She died at 7:30 p. m.

Case 2.—*Family and Past History.*—D. M., a Negro, was born in North Carolina in May 1908 and completed the seventh grade of elementary school. During childhood he had no unusual illnesses. As a rule he was moderate in his habits but periodically drank whisky heavily. In June 1939 signs of early syphilis developed, for which he was treated by the intravenous injection of 1 Gm. of mapharsen within a five day period. He had no complications, and during the period of observation the serologic reactions of the blood remained positive. In October 1939 a generalized papular eruption developed and he again was given intravenous injections by the drip method, 1.2 Gm. of mapharsen being administered within five days. No complications arose, and he was treated and observed further at the New York Hospital Clinic. The serologic reaction became negative in January 1940. In September 1942 the clinic reported that physically he showed no evidence of syphilis. The Wassermann reaction of the blood was negative, and that of the spinal fluid was also negative except for a 2 plus reaction in the last two tubes. Previously the reaction had been negative throughout. This change in the reaction of the spinal fluid was thought to be an artefact. The patient was described as good natured, friendly and sociable. The family history was stated to be negative for nervous and mental disease.

Psychosis.—Little exact information could be obtained from the patient's associates, but it was thought that he had become mentally ill about one month before his admission to the state hospital, on Nov. 25, 1942. He caused a disturbance at his home, but had not been drinking. At the hospital he expressed grandiose and persecutory delusions and admitted having auditory hallucinations of a religious character. He cooperated well and was correctly oriented in all spheres. The first physical examination made on admission disclosed some slurring of test phrases and perioral tremor. However, the pupils were round and regular and reacted well to light and in accommodation, and the deep reflexes were active and equal on the two sides. Physical examination otherwise revealed nothing significant. His blood pressure was 104 systolic and 62 diastolic. On Dec. 9, 1942 the Wassermann reactions of the blood and spinal fluid were reported to be completely negative. At this time he showed no perioral tremor, but his speech was a little slurred. He showed no sensorial defects, but was manneristic and at times silly. The diagnosis was dementia precox, paranoid type.

Electric Shock Treatment.—On Jan. 13, 1943, he received 90 volts for one-tenth second and had a petit mal reaction. He was soon ambulatory and showed no unusual reaction. On January 15 he received 100 volts for one-tenth second and had a typical grand mal convulsion. One hour later he was ambulatory and complained only of nausea and headache. He ate, and later in the morning he returned to his ward, where he was ambulatory. On January 17 he was fed by tube at 10:30 a. m. because he had been eating poorly. He appeared to be comfortable, however, and one hour later was fed by spoon. At noon he took liquid nourishment and engaged one of the nurses in conversation. At this time he had no physical complaints. He was first seen to be in distress at 1 p. m., when he appeared pale and was observed to be turning from his back to his abdomen in a restless manner. He retched and expectorated a little blood-streaked saliva, but did not cough or vomit. He made no complaints and cooperated well. The temperature was 101 F. and the pulse rate 88; respirations occurred at a frequency of 36 a minute and were labored. In a few minutes his eyes took on a glazed appearance, and he stared at the ceiling. At 1:30 p. m. he was moribund, and a few minutes later he died.

Autopsy.—Autopsy was performed by Dr. Reider Trygstad, of the Central Islip State Hospital, two hours after the patient died. The report follows.

General Inspection: The body was that of a Negro aged about 30 or 35. Nutrition was fair and the musculature good. There were no deformities. Rigor mortis had not set in. The conjunctiva was clear, and the pupils were equal and in middilation. There was no edema of the ankles or the face.

Cranial Cavity: The calvarium was of thin, firm bone. The amount of cerebrospinal fluid was decreased. The brain was swollen. The pial vessels were notably injected. The pia mater was thin and transparent. The basal vessels were small and thin walled. Preliminary section showed slitlike ventricles. The brain weighed 1,210 Gm. The pituitary gland and pituitary fossa were normal.

Thorax: The pectoral muscles were an intense red. Both lungs were noticeably expanded and were free of adhesions. When the hand was placed in the thoracic cavity, a frothy, blood-tinged fluid escaped from the mouth. The right lung weighed 1,280 Gm. and the left lung 1,270 Gm. The pleural surfaces were clear. There were no petechiae. Sections of the lungs showed an extensive degree of engorgement of the air sacs, with frothy, slightly blood-tinged fluid. The lungs were otherwise normal. The heart was small and weighed 270 Gm. The epicardial surface of the left ventricle showed a few small petechiae. The valves of the heart, the coronary vessels and the heart muscle appeared normal on section. No clots were present. The aorta and the pulmonary artery were both small in caliber. The circumference of the aortic valve was 8.5 cm. and that of the pulmonary valve 9 cm. The aorta showed no evidence of sclerosis or aortitis, and the larger vessels were normal.

Abdomen: There was no subcutaneous or subperitoneal fat. The serosa of the intestine was moist and glistening. The vessels were slightly injected. The spleen was of average size, and the cut surfaces were of normal appearance. The gastrointestinal tract was normal. The stomach contained about 3 pints (1,500 cc.) of the tube-fed mixture. The mucosa was of normal appearance. The liver was of average size; from cut sections there exuded an increased amount of blood. The gallbladder contained one stone, which was free. The vessels of the pancreas were slightly injected. The left adrenal gland was of average size and pattern, and the medulla was congested. The right adrenal gland was small, but of normal pattern. The kidneys were of average size; the capsules, especially the capsule of the left kidney, were slightly adherent, and the cortical surfaces were smooth. Cut sections showed normal markings. The urinary bladder contained about 4 ounces (118 cc.) of clear urine. The prostate appeared normal, and the genitalia were hypoplastic.

Summary: The significant changes were edema of the brain, pronounced edema of the lungs and hypoplasia of the circulatory system.

Anatomic Diagnosis.—The probable cause of death was asphyxia, with acute edema of the lungs and brain due to circulatory failure, the result of electric shock therapy.

General Histologic Report.—All of the tissues appeared essentially normal.

Neuropathologic Report.—The brain was studied by Dr. Armando Ferraro, of the New York State Psychiatric Institute and Hospital. His report and discussion follow.

Blocks were taken from various areas of the central nervous system, i. e., the frontal, occipital, parietal and temporal cortex; the basal ganglia; the mesencephalon; the pons; the cerebellum, and the medulla oblongata. The usual neuropathologic technics were used—chiefly the Nissl stain for nerve cells, the Spielmeyer method for myelin sheaths, scarlet red for fatty products of degeneration, the Bielschowsky method for neurofibrils and hematoxylin and eosin for general study.

The impression was that of a pathologic condition of the central nervous system of organic type. The most conspicuous changes seemed to indicate a degenerative process, the result, presumably, of vascular involvement.

The pathologic changes in the vessels were represented by diffuse congestion of varying degrees and, above all, by thickening of the walls of the blood vessels and endarteritis, involving the small blood vessels. Presumably as the result of this pathologic process in the vessels, there was diffuse degeneration of nerve cells in various areas. In these areas, in differing degrees, nerve cells had undergone various types of degeneration—chiefly, however, a process that closely resembled the so-called ischemic change. Occasional nerve cells disclosed chromatolysis and gradual disintegration. This degeneration of nerve cells led to scattered areas with poverty of nerve cells and some disturbance of cytoarchitecture.

As a part of the degenerative process involving the nerve cells were a considerable degree of satellitosis, and, even more important, a conspicuous amount of neuronophagia, in which proliferated glial elements actually invaded cells undergoing degeneration.

Throughout the white matter of the cortex, but varying in intensity, was a definite increase of glial nuclei. The oligodendrocytes seemed to be particularly increased and were accumulated in rows about the blood vessels. Here and there, particularly in the cerebellum and the medulla oblongata, collections of glial nuclei formed the so-called glial nodules. In the medulla oblongata, in the area of the tenth, and particularly the eighth, nerve, there was considerable increase of glial nuclei, and bilaterally, in the area of the descending root of

the trigeminal nerve, there occurred a small softening in which microglia and oligodendroglia cells, in various phases of reaction, were noticeable.

In the basal ganglia, the vascular changes were more pronounced, and blood vessels were undergoing hyaline degeneration. In addition, considerable calcification of blood vessels was noted in the internal capsule and the striatum.

Here and there in the occipital lobe were areas in which metabolic products of disintegration, such as amyloid bodies, were numerous, particularly in the vicinity of the posterior horn of both lateral ventricles.

Of importance in this case was the occasional presence of hematic pigment immediately surrounding the blood vessels. However, fresh hemorrhages, in which red blood cells were still well preserved, were not seen.

About some of the small blood vessels was a slight infiltration, consisting chiefly of lymphocytes.

The problem under discussion in this case concerns the relation of electric shock therapy to the pathologic changes in the central nervous system. The clinical history gave evidence of syphilitic infection, and the neuropathologic changes indicated a form of vascular syphilis, the most probable type of which was the so-called endarteritis of the small blood vessels. Inflammatory changes were few, it is true, but here and there small perivascular infiltrations of lymphocytes were apparent. This manifestation of inflammation, however, was of minor intensity. The meninges disclosed a considerable number of chromatophores, and the blood vessels showed both calcification and hyaline degeneration, all changes in accord with a possible diagnosis of cerebrovascular syphilis.

Only the occasional punctiform hemorrhages could be related to the action of the electric shock. Here, also, the previous involvement of the blood vessels by a pathologic process must be considered, damage which made easier the extravasation of blood. The latter was perhaps related to the first of the two electric shocks, since only blood pigment, and not fresh red blood cells, was to be seen.

With respect to the vascular congestion, asphyxial phenomena preceded death, and the asphyxia was related to congestion of the lungs and may have provoked the vascular distention. The neuropathologic study of this case failed therefore to reveal evidence of any relation between the pathologic changes and electric shock therapy except for the few punctiform hemorrhages, which may have been induced by the convulsive seizure. The entire pathologic picture points to a preexisting pathologic process, presumably of syphilitic origin.

COMMENT

Several investigators have shown, with the aid of laboratory procedures, that electric shock treatment creates a disturbance in cerebral function. Pacella, Barrera and Kalinowsky [6] stated that changes in the electroencephalographic pattern occur in all cases and may persist several months if grand mal convulsions have been produced. Levy, Serota and Grinker [7] claimed that such alterations occur in 50 per cent of treated patients; they agree that the changes may last several months. They stated that changes in intellectual function occur in 45 per cent of cases but declared that mental improvement is not dependent on the presence of such changes, as demonstrated electroencephalographically or by other means.

Alpers and Hughes,[8] in experiments with cats, discovered that hemorrhage, either punctate or of a more extensive character, is the most common lesion and may occur anywhere in the brain. They noted loss of cells and fibers in the region of extravasations. They expressed the opinion that there is no relation between the number of shocks and the severity of changes in the brain. Heilbrunn and Weil [9] made similar observations on rabbits. They noted multiple small hemorrhages throughout the brain, produced by rupture of the vessel walls, combined with edema, injury to ganglion cells and a proliferative glial reaction of the surrounding tissues. They expressed the opinion that the danger of electric shock treatment lies not in generalized destruction of ganglion cells, which they did not see, but in the possibility of multiple hemorrhages, followed by local repair.

Thus far, autopsy reports have seldom been adequate; so one is still groping in the dark. In 1 of the 3 cases for which Ebaugh and his associates tabulated data with autopsy observations, the patient was 75 years old, and there was enough evidence of advanced arteriosclerosis to obscure any pathologic changes that might have been due to the three treatments the patient received. Their own 2 cases had many features in

6. Pacella, B. L.; Barrera, S. F., and Kalinowsky, L.: Variations in Electroencephalogram Associated with Electric Shock Therapy, Arch. Neurol. & Psychiat. **47**: 367-384 (March) 1942.

7. Levy, N. A.; Serota, H. M., and Grinker, R. R.: Disturbances in Brain Function Following Convulsive Shock Therapy, Arch. Neurol. & Psychiat. **47**:1009-1029 (June) 1942.

8. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat. **47**:385-398 (March) 1942.

9. Heilbrunn, G., and Weil, A.: Pathologic Changes in the Central Nervous System in Experimental Electric Shock, Arch. Neurol. & Psychiat. **47**:918-930 (June) 1942.

common, but the significance of the observations suffered in some respects because the patients were 57 years of age. Nerve cell degeneration, of variable degrees, increased gliosis and ischemic changes in scattered cells were noted in both cases. The brain of the patient who had thirteen treatments showed one petechia on gross inspection and an occasional perivascular area of pigment, but no signs of fresh blood, while the brain of the second patient, who received only three treatments, presented none of these changes. The latter, too, showed cellular changes with neuronophagia in the dorsal nucleus of the vagus nerve, together with *Gliarasen*. Both patients, surprisingly, received relatively small doses of electric current.

The pathologic picture in the case reported here, unfortunately, was complicated by the syphilitic process, but it should be kept in mind that there was little inflammatory change. Prior to treatment the Wassermann, mastic and benzoin reactions of the spinal fluid were negative, and the total protein was only 35 mg. per hundred cubic centimeters. The diffuse cellular degeneration, with disturbed cytoarchitecture, the ischemic changes in cells and the increase in glia cells—all of which were noted in the cases reported by Ebaugh and associates—may well have been due to the syphilitic process. Certainly, the perivascular infiltration, the hyaline degeneration of vessels and the amyloid bodies speak for vascular syphilis. Some of these changes may have been due to the intensive treatment with arsenicals in 1939. However, two features of the pathologic process in this brain deserve closer consideration. In the areas of the eighth and tenth nerves "there was considerable increase of glial nuclei, and bilaterally, in the area of the descending root of the trigeminal nerve, there occurred a small softening in which microglia and oligodendroglia cells, in various phases of reaction, were noticeable." Ebaugh and associates reported somewhat similar changes in the medulla of the patient who received three treatments. Consequently, one may surmise that these changes were produced by the electric current, which notably affects the respiratory center, or were already present as a result of the syphilis and were aggravated by the electric treatment. Progressive alterations occurring in the medulla after the second treatment may have resulted in the clinical picture immediately preceding death.

The second feature worthy of close attention is one which Ebaugh and associates noted in 1 of their cases, namely, the presence of perivascular hematic pigment, an indication of the occurrence of punctiform hemorrhages. Hemorrhages of this type were commonly observed in cats and rabbits, but in my second case and in Ebaugh's case fresh hemorrhages were not seen. The presence of perivascular pigment, however, is presumptive evidence of previous hemorrhage, and it may be surmised that the bleeding was the result of the syphilitic process already present in the vessels. Extravasation during a convulsion would conceivably be easier through the wall of a damaged vessel than through the wall of a healthy one. This evidence emphasizes the need of selection for treatment of patients who are free from the taint of vascular, as well as cardiac, involvement. Of course, the patient would not have been treated if the laboratory tests had given positive evidence of syphilis. Perhaps the fact that the Wassermann reaction of the blood was once positive should have been regarded as a contraindication.

No definite conclusion can be drawn with respect to the first case because of the absence of autopsy evidence. However, the acute nature of the patient's death, which followed so closely on her treatment, makes it logical to suspect some connection between the two events. It is possible that in this patient, as in a few of the cats studied by Alpers and Hughes, more extensive hemorrhages occurred in the hypothalamic region, sufficient to cause the hyperpyrexia and status epilepticus. The fact that the patient died one week after her last treatment speaks against this possibility, but the exact time of occurrence of hemorrhage after treatment is not known. Further, it is possible that, among other areas injured, the current produced damage to the cells in the region of the already labile heat-regulating center. These changes could have been associated with punctate hemorrhages and subsequent edema to produce the same result. While it is unwise to speculate too much about this case, I feel that one is only avoiding the issues involved if one disregards this death or attributes it merely to "excitement and exhaustion." Fatalities of this nature warrant continued study.

The fact remains that even after autopsy the cause of death sometimes remains unknown. In the first case reported by Ebaugh and associates death was due to coronary thrombosis, but the cerebral changes, although more extensive than those in their second case, seemed insufficient in themselves to cause death. Of their second case they stated:

> . . . . The changes in the brain cannot be considered directly responsible for the death. They are indicative

of some damage suffered by the brain during the shock treatment, but they do not answer satisfactorily the question of the cause of death.

Similarly, in the case presented here the cause of death was obscure. Grossly and microscopically the organs were normal, and the changes in the brain were compatible with longer life. The answer to the riddle may lie in the possibility that in selected cases there occur certain irreversible intracellular changes which no one has yet been able to fathom.

SUMMARY

Of 2 patients whose deaths were associated with electric shock treatment, the first died one week after her fourteenth treatment in a hyperpyretic state associated with status epilepticus. The second patient died two days after his second treatment. Autopsy in the second case disclosed evidence of cerebrovascular syphilis and other changes which were possibly due to the treatment itself. However, the alterations were not sufficient to account for death. A review of some of the pertinent literature indicates that the cause of death after electric shock treatment is still obscure. Selection of patients for treatment should not be indiscriminate, especially in the face of an unpromising prognosis. Electric treatment has attendant serious dangers and should not be given to patients with a history of vascular or cerebral disease.

Central Islip State Hospital.

TREMOR AND THE BABINSKI SIGN IN ALCOHOLIC PATIENTS

INCIDENCE AND INTERPRETATION

ARNOLD P. FRIEDMAN, M.D., AND JAMES E. ROY, M.D.

BOSTON

Alterations of cerebral function in alcoholic patients are evidenced by confusion, disordered speech and convulsions. In spite of these manifestations of cerebral dysfunction, tremor is not always present, and the Babinski sign is rare. To determine the incidence of tremor and the Babinski sign in alcoholic psychoses, we carefully examined 200 patients, all of whom were addicted to prolonged and excessive use of alcohol in various forms.

MATERIAL AND OBSERVATIONS

The material consisted of 200 adults, ranging in age from 21 to 65, with histories of various degrees of alcoholism, who were admitted to the Boston Psychopathic Hospital between November 1940 and June 1943 for alcoholism. In tests for the Babinski sign, the criteria employed were essentially those laid down by Babinski in *Semaine médicale*. The patient was well relaxed, with the eyes closed, the legs extended and the feet resting on the bed near its outer edge, or with the legs lifted and held by the examiner. In all cases it was ascertained that free movement of the big toe was possible. The stimulation was vigorous and was applied to the outer part of the sole of the foot. A constant extension of the large toe was considered a Babinski sign. Fanning of the toes was not considered an essential part of the Babinski sign in this study.

Of the patients studied, a Babinski sign was elicited in 16, and gross tremor, particularly in the upper extremities, in 87. Of the 16 patients, the Babinski sign was typical and constant in 5 and atypical in 11. An atypical response consisted either in no movement of the great toe or in partial dorsiflexion, occurring unilaterally, while a clearcut normal response was obtained on the other side. Tremor was present in 4 of the patients with a constant Babinski sign and in 10 of the patients with an atypical sign. The 5 patients who exhibited a constant Babinski sign showed additional signs and symptoms, an indication of pronounced abnormalities of the central nervous system. A brief description of the 5 cases follows.

CASE 1.—A white man aged 56 was admitted to the hospital because of visual hallucinations and threatening behavior. He had been drinking heavily since the age of 27 but had stopped three weeks prior to admission. There was a history of a previous attack of depression. A week prior to admission he became violent, wanted liquor, broke a window, called his sister names and expressed grandiose ideas.

On admission he was restless and overactive, and speech was incoherent and irrelevant. He expressed grandiose delusions, was completely disoriented for time and gave a poor account of his past life. The impression was that of dementia paralytica, but lumbar puncture, including serologic tests, gave negative evidence.

The blood pressure was 200 systolic and 100 diastolic. Neurologic examination revealed atrophy of the left optic nerve, chorioretinitis involving both eyes, absence of the pupillary reflex to light and internal strabismus. There was tremor of both upper extremities. The reflexes were hyperactive in the trunk and the lower extremities, and a Babinski sign was elicited bilaterally.

The patient showed no improvement and was committed to a state hospital at the end of one week.

CASE 2.—A white man aged 50 was admitted to the hospital via the courts because of threats. He had had previous admissions to the hospital for alcoholism and for epilepsy. The epilepsy had been characterized by typical grand mal convulsions occurring at frequent intervals over a period of twenty years. Studies during this time (including lumbar punctures) revealed no cause for the convulsions.

Examination showed tremor of the upper extremities. The reflexes were hyperactive in both the upper and the lower extremities, and a Babinski sign was elicited on the left side. The mental status was not remarkable except for irritability.

CASE 3.—A white man aged 29 was admitted to the hospital because of confusion. He was known to have been alcoholic for several years.

Examination of his mental status on admission showed tremulousness, misunderstanding of commands, disorientation, auditory hallucinations and poor cooperation.

General physical examination revealed a smooth tongue, enlargement of the liver and cutaneous changes consistent with severe avitaminosis. (The changes attributed to avitaminosis disappeared with treatment.) Neurologic examination showed weakness of the extremities, hyperactive reflexes, myoclonic movements of all extremities and a Babinski sign on both sides. Tremors were present in the upper extremities. There were sweating, coldness and cyanosis of the hands and feet. A few days after admission he had epileptiform seizures of tonic type ("cerebellar fits").

CASE 4.—A white man aged 56 was admitted to the hospital because of confusion and increased activity. Three days prior to admission he fell unconscious. He was removed to another hospital, where he was confused, complained of headache and, after medication, attempted to sever his penis. He was known to have been alcoholic for several years.

From the Boston Psychopathic Hospital and the Department of Psychiatry, Harvard Medical School.

Neurologic examination revealed signs of meningeal irritation, including positive Brudzinski and Kernig signs. The reflexes were hyperactive in both upper and lower extremities. The Babinski sign was elicited bilaterally. Lumbar puncture revealed grossly bloody fluid. A diagnosis of spontaneous subarachnoid hemorrhage was made. Bleeding continued, and the patient was transferred to another hospital, where he died.

CASE 5.—A white man aged 33, who was known to have been alcoholic for many years, was admitted to the hospital because of characteristic delirium tremens. He had previously sustained an injury to the head of undisclosed severity and had been admitted to another hospital in a state of delirium.

Examination revealed a hematoma of the scalp, unequality of the pupils, which reacted poorly to light, tremor of the upper extremities and a Babinski sign bilaterally. Lumbar puncture showed clear, colorless fluid under normal pressure. However, serologic studies of the blood and spinal fluid gave positive reactions, and the colloidal gold curve was characteristic of dementia paralytica. When the delirium cleared, the patient showed a typical picture of this disease.

It should be noted that 11 patients had an atypical Babinski sign and that of this number 10 had accompanying tremor. This is in contrast to the figures for the other 174 patients in the series, only 73 of whom had tremor.

COMMENT

The mechanism of tremor associated with alcoholism has often been postulated to be cerebellar. In patients in the present series the signs and symptoms pointed to diffuse disorganization of the cortex as playing a part in the production of tremor, possibly through disturbance of the frontopontocerebellar tracts. In some patients the chemical activity of alcohol produced a picture akin to an anxiety state, with fears, apprehensions and coarse generalized tremors. These symptoms, together with the anxiety, disappeared rapidly as the effects of the alcohol diminished. This is in contrast to the picture characteristic of dementia paralytica, Wilson's disease (hepatolenticular degeneration) and other degenerative diseases, in which the tremor is maintained constantly, with only slight moderation by psychogenic factors. We interpreted the Babinski sign as a part of the defense reflex, and eventually as a part of the flexor reflex. Its presence indicates involvement of the corticospinal pathways, on either an anatomic or a functional basis.

The various pathologic syndromes of acute and chronic alcoholism are associated with lesions involving structures from the periphery to the cortex. That persons with considerable evidence of cerebral alteration presented no signs of damage to the pyramidal tract indicates the possibility of selective damage by alcohol to certain parts of the nervous system. Only in patients with evidence of other etiologic factors, such as syphilis of the nervous system, subarachnoid hemorrhage and pellagra, did signs of damage to the pyramidal tract appear. This may be because the main effect of alcohol is on the association tracts, rather than on the great projection fiber system. Mental aberrations, disturbances in speech, tremors and absence of signs of damage to the pyramidal tract may be explained by this hypothesis. A similar picture exists with some of the cortical and mixed degenerative disorders. The fact that patients with the Babinski sign had a higher incidence of tremor suggests more advanced involvement of the central nervous system, with beginning involvement of the projection fiber tracts.

It is noteworthy that in none of the 200 patients studied did the condition resemble the typical Wernicke syndrome, or polioencephalitis hemorrhagica superior (with extraocular palsies, pupillary changes and disturbances in consciousness).

CONCLUSIONS

The extreme rarity of the Babinski sign in patients with uncomplicated alcoholism is evidence that lesions of the corticospinal tract are rarely produced by alcoholism, and its presence should focus the attention of the examiner on factors other than alcoholism.

The absence of signs of involvement of the pyramidal tract in alcoholic patients may indicate selective action of alcohol on the central nervous system. In the cerebrum this action is probably chiefly on the association tracts, rather than the great projection fibers.

Tremor is present in a significant number of alcoholic patients with psychosis but is extremely variable in type and rhythm. Such tremor may be caused by alteration in the frontopontocerebellar mechanism, but sometimes it may be influenced or aggravated by associated anxiety.

Tremor is much more constant in patients who show an atypical Babinski sign than in alcoholic patients in general. This frequency of association might be taken as an indication in such patients of more advanced involvement of the central nervous system, with beginning disturbance in the projection fibers.

None of the 200 patients studied had a condition which answered the description of Wernicke's syndrome, or encephalitis haemorrhagica superior.

Boston Psychopathic Hospital.

Clinical Notes

A SIMPLE AUTOMATIC PNEUMOENCEPHALOGRAPH

CAPTAIN RAYMOND L. OSBORNE, MEDICAL CORPS, ARMY OF THE UNITED STATES

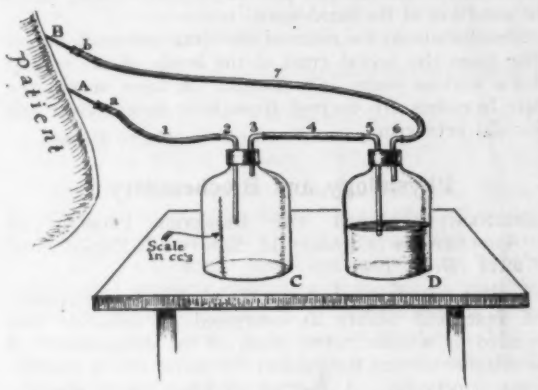
That air appears as a contrasting medium in the ventricles of the brain in roentgenograms of the skull was accidentally discovered by Luckett,[1] in 1913. Dandy,[2] in 1918, was the first to use air intentionally, when he introduced the gas directly into the ventricles. In 1919 he [3] injected air into the lumbar subarachnoid space to outline cerebral structures on the roentgenogram. This procedure he called encephalography. To avoid confusion with electroencephalography, it may better be designated as pneumoencephalography. If no block exists, the pneumoencephalographic method provides for admission of air into any intracranial space occupied by cerebrospinal fluid.

TECHNIC

In this paper there is described a simple automatic pneumoencephalograph which can be improvised from materials usually at hand in any hospital. Any two receptacles, a length of rubber tubing and one of glass, two lumbar puncture needles and two needle adapters comprise all that is necessary. Two empty Baxter Vacoliter infusion flasks are ideal, but fruit jars with suitable rubber stoppers will do, provided they are made air tight. The material is arranged into the system illustrated in the accompanying figure.

The patient is placed in a sitting position, leaning forward against the back of an inverted chair, which is cushioned with pillows. A double rachiocentesis with two needles is performed at the fifth and the fourth or third lumbar interspace in the usual way. The pneumoencephalographic system is filled with oxygen [4] by passing the gas through from *1* to *7*, and then the rubber tubing is closed off by pinching or with hemostats placed at *1* and *7*. Now tube *1* is attached by its glass adapter, *a*, to needle *A*, and a little cerebrospinal fluid is allowed to run into the bottle *C*. If it is desired to draw off more fluid than air,[5] the desired quantity may be drained off from the open needle before the system is connected. Then tube *7* is similarly attached to needle *B* by its adapter, *b*. The operation is then completed.

Now each drop of fluid displaces gas from bottle *C*, passes it through glass tube *3*, rubber connection *4* and glass tube *5* and washes it free of dust and contaminant in the water trap. The gas then bubbles out tube *6* and rubber connection *7* and into the intrathecal space through needle *B*. Since fluid is heavier than gas, gravity draws the cerebrospinal fluid down and allows the gas to rise; thus fluid continues to drain out of needle *A* and the gas to pass in through needle *B*. The gas accumulates in the subarachnoid system of the skull



Drawing of the pneumoencephalographic apparatus.

and displaces more fluid down and out. The procedure is completed when the automatic system stops operating, for the subarachnoid space is then drained. The roentgenogram is then taken immediately.

ADVANTAGES

In the closed method there is less mechanical change in the subarachnoid space; fluid is displaced drop by drop, not ounce by ounce, and intrathecal pressure fluctuates little. The headache following the procedure is less severe and the postoperative course shorter. After the machine is connected and running, the operator may observe his patient, for his hands are free. The machine will automatically complete the procedure and stop itself. The apparatus costs nothing, for it is made of scrap materials found in any hospital.

From the Section of Neuro-Psychiatry, Station Hospital, Army Air Base, Lincoln, Neb.

1. Luckett, W. H.: Air in the Ventricles of the Brain Following a Fracture of the Skull, J. Nerv. & Ment. Dis. **11**:326, 1913.

2. Dandy, W. E.: Ventriculography Following the Injection of Air into the Cerebral Ventricles, Ann. Surg. **68**:5, 1918.

3. Dandy, W. E.: Roentgenography of the Brain After the Injection of Air into the Spinal Canal, Ann. Surg. **70**:397, 1919.

4. Atmospheric air or various gases may be used. Oxygen is preferable because it is absorbed rapidly and is less irritating.

5. Gas expands in volume with increase in temperature, in accordance with the Gay-Lussac law; therefore many operators draw off more cerebrospinal fluid than the volume of the gas they admit to the subarachnoid space.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

AN EXPERIMENTAL STUDY ON THE ORIGIN OF THE SENSORY NEURONES AND SHEATH CELLS OF THE IXTH AND XTH CRANIAL NERVES IN AMBLYSTOMA PUNCTATUM. C. L. YNTEMA, J. Exper. Zool. **92**:93 (Feb.) 1943.

Previously described experimental methods were used in the investigation of the origin of the glossopharyngeal and the vagus nerve The ninth and tenth lateral line ganglia arise from dorsolateral placodes, while the visceral ganglion of the ninth nerve comes from the second epibranchial placode. The anterior visceral ganglion of the tenth nerve arises from the third and fourth epibranchial placodes, and the posterior visceral ganglion of the tenth nerve, from the fifth epibranchial placode.

The postbranchial neural crest, which is medial to the fourth and fifth somites, gives rise to the root ganglion of the tenth nerve, while from the neural crest which lies medial to the anterior part of the sixth somite arises the ganglion of the third spinal nerve.

Sheath cells on the roots of the ninth and tenth nerves arise from the neural crest at the levels of the origins of the various roots. Sheath cells on these nerves and their branches are derived from both neural crest and placodal ectoderm.

REID, Boston.

Physiology and Biochemistry

CHOLINESTERASE AND THE BEHAVIOR PROBLEM IN AMBLYSTOMA. CHARLES H. SAWYER, J. Exper. Zool. **92**:1 (Feb.) 1943.

A close correlation between the cholinesterase content and functional ability as expressed by behavior was revealed by a quantitative study of the development of the enzyme content throughout the larval life of Amblystoma punctatum. A method of alkalimetric microtitration of the acetic acid liberated on the hydrolysis of acetylcholine was used. This method was sensitive to 5×10^{-9} mols of ester (0.9 micrograms of acetyl choline chloride).

The small amount of the esterase found in the premotile embryo did not increase during the early flexure and coil stages but rose sharply at the beginning of the nontetanic S flexure stage. The enzyme continued to increase during the period of the more rapid movements of the swimming stages.

Larvae reared in solutions of cholinesterase inhibitors showed profound changes in physiologic activity, which were found to depend on the degree of inhibition of the enzyme. On removal of the animal from the inhibitor solution the recovery of physiologic capacity and that of enzymic activity paralleled each other.

The author concludes that cholinesterase content is a biochemical criterion of functional capacity in the neuromuscular apparatus and that the physiologic development of this system can be quantitatively assayed in terms of its esterase activity.

REID, Boston.

EFFECT OF 180 DEGREE ROTATION OF THE RETINAL FIELD ON VISUOMOTOR COORDINATION. R. W. SPERRY, J. Exper. Zool. **92**:263 (April) 1943.

In 15 newts both eyeballs were rotated 180 degrees on the optic axis, the optic nerves being left intact. In 14 newts only one eyeball was rotated, while the other eye was either excised or left in the normal position. This rotation resulted in complete inversion and reversal of visual perception, which was manifest in deliberate erroneous reactions and various abnormal performances directly related to retinal rotation. There was also a dorsoventral reversal in chromatophoric adaptation.

The animals with reversed vision were at a greater disadvantage than the totally blind control newts. The maladaptive visuomotor coordinations persisted in all cases during the four and a half months of the test period, without any sign of inhibition or correction by reintegration of the central nervous system.

The results demonstrate a rigidity of mechanisms for central coordination in the visuomotor system of urodeles comparable to the implasticity of spinal organization present in amphibians and rats.

REID, Boston.

THE EFFECT OF PROSTIGMINE AND ACETYLCHOLINE ON DENERVATED MUSCLE. RUDOLF ALTSCHUL, J. Nerv. & Ment. Dis. **97**:549 (May) 1943.

Although there are theoretic reasons for the employment of prostigmine with other diseases of the central and peripheral nervous systems, its use has been accepted only in treatment of myasthenia gravis and postoperative paresis of the bowel and bladder. With the idea of testing the value of the drug in treatment of injuries of the motor nerves, the author attempted to determine the effect of injections of prostigmine and acetylcholine in hastening recovery from lesions of the lower motor neuron. In 18 animals (8 cats and 10 rabbits) the lateral popliteal nerve, and in some animals the sciatic nerve also, was avulsed and treatment started immediately with intramuscular injections of prostigmine methylsulfate (in a dose of from 0.2 to 0.6 cc. of a 0.5 per cent solution) and subcutaneous injections of acetylcholine (from 0.00025 to 0.0065 Gm.). The effect of treatment was judged clinically by observation of the spreading reflex of the toes and anatomically by loss of weight of the innervated muscle and by histologic examination of the severed nerve trunk and atrophic muscle.

There was no clear difference in loss of weight between muscles of treated and those of untreated animals. Histologic changes in the denervated muscles were greater in the controls than in the treated animals and greater in the rabbits than in the cats. The proliferation of connective tissue which would be expected in atrophic muscle was slight or absent in treated cats. Thus, histologic comparison of the denervated muscles in cats showed greater changes in the untreated than in the treated animals, but as measured by loss of weight the difference was not apparent. No such results were obtained in the rabbits. In addition, there were notable differences in the reactions to the drugs of different animals of the same species, while various muscle groups also reacted differently. The author believes that experiments of this type should be repeated, if possible with larger doses of acetylcholine.

CHODOFF.

Neuropathology

OLIGODENDROGLIOMATOSIS OF THE CEREBROSPINAL PATHWAY. DIANA J. K. BECK and DOROTHY S. RUSSELL, Brain **65**:352, 1942.

In recent years oligodendrogliomas, which in the past were regarded as benign, have been observed by several investigators to take on malignant features. Beck and Russell report 4 instances of metastatic spread of an oligodendroglioma along the cerebrospinal pathway. In these 4 cases the tumor spread diffusely throughout the subarachnoid spaces, including those of the spinal cord in the 3 instances in which the cord was examined. The primary tumor abutted on the ventricular system in all but 1 case. Dissemination of the tumor cells was spontaneous, though it was probably accelerated by operative intervention in 1 case. In the latter case ventriculographic examination revealed dilatation of the lateral and third ventricles before operation, and it may therefore be inferred that meningeal deposits were already present at this time. Two of the 4 cases reported were those of children, the shortness of the clinical history and the macroscopic appearance of the meninges being reminiscent of medulloblastoma. The adults had a longer history and the macroscopic change in the meninges strongly resembled chronic arachnoiditis. In all 4 cases the length of the clinical history was, in fact, directly proportional to the degree of meningeal fibrosis. Oligodendrogliomas, therefore, may vary widely in their behavior. They may proliferate as actively as any of the more malignant gliomas; on the other hand, the metastases may undergo little active proliferation, but promote, rather, meningeal fibrosis.

Diffuse mucinous change in the stroma in oligodendrogliomas is pointed out as of diagnostic importance, a special search in other types of metastasizing gliomas failing to reveal evidence of mucin.

Clinically, a variable degree of hydrocephalus occurred in all cases in which the cerebrospinal fluid pressure was persistently high. The protein content of the fluid was high, but few cells were noted. There was remarkably little involvement of cranial nerves, considering the extensive infiltration at the base of the brain. However, the first and second cranial nerves were affected in 3 cases.

High voltage roentgen therapy failed to confer any benefit in 3 cases. This accords with the increasingly prevalent opinion that the oligodendrogliomas, as a class, are not susceptible to irradiation.

SHENKIN, Philadelphia.

Psychiatry and Psychopathology

CLINICAL STUDIES IN SCHIZOPHRENIA. C. MACFIE CAMPBELL, Am. J. Psychiat. **99**:475 (Jan.) 1943.

Campbell studied 9 patients who manifested schizophrenic surrender. The outstanding factors in this group were the constitutional inadequacy and the unfavorable external factors. No physical factors could be elicited which satisfactorily explained the deterioration. Campbell noted that in the course of deterioration, when superior functions fell into abeyance, reactions of a lower neurologic order appeared. No special manifestation of basic urges was evident, and the condition was one of defect rather than of conflict. The patients surrender and accept life at a lower, automatic level. This surrender is the response of underprivileged, frustrated persons to the challenge of life.

FORSTER, Philadelphia.

STUDIES ON THE PROGNOSIS IN SCHIZOPHRENIC-LIKE PSYCHOSES IN CHILDREN. R. S. LOURIE, B. L. PACELLA and Z. A. PIOTROWSKI, Am. J. Psychiat. **99**:542 (Jan.) 1943.

Lourie, Pacella and Piotrowski studied 20 children who at some time before the age of 12 years experienced psychotic episodes classifiable as schizophrenia of childhood. The group comprised 15 boys and 5 girls who presented a psychotic picture characterized by deterioration from a previous level. The average period of hospitalization was ten months. The average follow-up period was eight years. At the end of the periods of observation the following levels of adjustment were observed: An apparently normal adjustment had been made by 4 patients; fair to borderline adjustments, by 5 patients, and low grade adjustments, by the remaining 11 patients. Of the last group, 3 manifested reactions of adult schizophrenia, 5 maintained their level at the time of hospitalization or deteriorated further and in 3 an organic basis was established. In the vegetative sphere, it was striking that all patients who failed to improve remained physically infantile. Anxiety, when associated with resignation, was of poor prognostic significance. Psychometric data with regard to intellectual and perceptual assets offered prognostic aid. The patients capable of cooperation in the Rohrschach tests showed improvement. Electroencephalographic studies showed no definite correlation with the psychotic picture.

FORSTER, Philadelphia.

THE SIGNIFICANCE OF PSYCHOLOGICAL RESEARCH IN SCHIZOPHRENIA. KURT GOLDSTEIN, J. Nerv. & Ment. Dis. **97**:261 (March) 1943.

Goldstein points out that a mental change is characteristic of schizophrenic patients but that not all patients with a condition clinically diagnosed as schizophrenia show it. Psychologic investigation may be able to differentiate patients exhibiting this change and thus indirectly aid in prognosis. Psychologic studies, moreover, may be of aid in evaluation of the quality of recovery after treatment and may serve to indicate the need of further psychotherapy.

Earlier work of this nature emphasized minute analysis of single psychologic capacities rather than the experimental study of changes in the total personality, which is the modern trend. From studies of the latter type on persons with lesions of the brain, Goldstein distinguishes between two kinds of human behavior, the abstract and the concrete. These are considered as capacity levels of the total personality, concrete behavior being realistic, stimulus bound and immediate, while abstract behavior is detached, categorical and conceptual. There are various degrees of each kind. The healthy person combines the two types of behavior and can shift voluntarily from one to the other. In certain diseases of the brain the capacity for abstract behavior is impaired, and the patient's behavior becomes reduced to a concrete level. This is considered as the characteristic change in patients with injury to the brain.

Employing the same general concept, Vigotsky devised a sorting test through the use of which he observed a similar impairment of the attitude toward the abstract in schizophrenic patients. In his work with such subjects, Goldstein prefers to use a battery of tests, including a modification of the Kohs block designs. His results are in agreement, in principle, with those of Kasanin and Hanfmann, and of Cameron, namely, that some schizophrenic patients present a characteristic impairment of the attitude toward the abstract.

When viewed from this approach, certain schizophrenic symptoms become understandable. Thus, some of the strange words used by the schizophrenic patient are comprehensible when they are considered in relation to the concrete situation which the patient experiences at the moment. There is an absence of generic or categorical words. Goldstein believes that peculiarities of language associated with schizophrenia have been erroneously considered as expressions of symbolic or metaphorical thinking. To understand the language of schizophrenic persons, the observer must discover and understand the special concrete situations in which the patient is living.

Another difficulty in the thinking of schizophrenic patients, as in that of patients with organic lesions of the brain, is loss of constancy and definiteness in the conception of the structure of objects. This is ascribed to impairment of the "normal" figure-ground formation, to the patient's inability to place the proper significance in the figure part of experience and abstract it from the ground. Many illusions and delusions of schizophrenic persons originate in this way, since, owing to deficient figure-ground formation, objects or situations which can be grasped as concrete come abnormally into the foreground and the patient gives an answer which appears to the normal person as a defect in recognition. An outstanding symptom is the disappearance of the normal boundaries between the ego and the outer world.

Although Goldstein believes that equivalent functional changes can be produced by organic and by psychologic derangement, he does not draw conclusions as to the identity of the underlying processes in organic disease and in schizophrenia. While both conditions show impairment in the attitude toward the abstract, the trend toward the concrete in patients with somatic disturbance is of a more simplified and inane form than that of the schizophrenic patient, which has a richer and more individual flavor.

Whether the impairment toward the abstract associated with schizophrenia is a primary or a secondary phenomenon cannot be definitely stated. The similarity in the changes in patients with organic disease and those in schizophrenic patients points to the probability that a somatic factor is involved in schizophrenia.

As long as the impairment persists in the attitude toward the abstract, the usual psychotherapeutic procedure is doomed to failure. Thus a more direct, concrete communication with the patient, based on empathy and cooperation with him, is necessary. Shock therapy may be able temporarily to lift the impairment and permit psychotherapy to be effective. It is at this time that the battery of tests employed by the author may be useful in indicating the accessibility of the patient and the type of psychotherapy to be employed.

CHODOFF.

NOTES ON THE PERSONALITY OF PATIENTS WITH MIGRAINE. LOWELL S. TROWBRIDGE, DOROTHY CUSHMAN, M. GENEVA GRAY and MERRILL MOORE, J. Nerv. & Ment. Dis. **97**:509 (May) 1943.

Migraine is a symptom complex rather than a disease, occurring frequently in otherwise healthy persons, often of high intelligence, and showing a strong familial tendency. In addition, there is the suggestion of an arrest in psychosexual development in many subjects with the disturbance. Of 37 women with the disorder who were studied by the authors, not one had made a successful heterosexual adjustment, and in all the libido appeared to be weak or poorly organized. The 13 men who were included in the series were reticent in discussing sexual adaptation and seemed to be lacking in sexual curiosity. Headaches first appeared at that moment in life when the victim was faced with an initial adult responsibility. The migrainous patient is deliberate in judgment, often indecisive, insecure, perfectionistic and compulsive, sensitive, anxious and quickly discouraged. Fromm-Reichmann expressed the belief that persons with migraine suffer from unresolved ambivalence and that in their effort to repress their hostility toward loved persons they convert it into the characteristic symptoms. The authors feel that the histories of their patients are similar to those of patients with frank psychoneuroses and of persons who are extremely maladjusted, and they suggest that the individual patient displayed his particular symptoms either because of his migrainous constitution or because his predisposition to migraine was activated by his special problems. Despite some belief to the contrary, there is no evidence that migraine affects brain workers more than laborers.

The Bell adjustment inventory, given to 4 male and 12 female patients suffering from migraine, revealed that they were normally adjusted to their homes, unsatisfactorily adjusted with regard to health, timid and retiring, poorly adjusted emotionally and well adjusted in their occupational environment. From these results it is seen that the migrainous patient tends to be similar to the psychoneurotic patient and that psychotic trends are absent.

CHODOFF.

PEYOTE INTOXICATION. WALTER BROMBERG and CHARLES L. TRANTER, J. Nerv. & Ment. Dis. **97**: 518 (May) 1943.

Peyote (Lophophora Williamsii and Anhalonium Lewinii) is a small, greenish cactus containing at least nine alkaloids. Its use produces characteristic physical, mental and visual phenomena of a universal type. With peyote intoxication there occurs an incessant flow of visions of infinite beauty, of both color and form, followed by horrible and grotesque appearances. The sense of time is lost, and after a time feelings of religious exaltation may appear. Two distinct types of reactions occur in the same person. In one, there are nausea, anxiety, feelings of bodily change, with fear of dissolution, and frightful visions; in the other, a feeling of religious peace and contentment and euphoria. The sensations experienced resemble those derived from the smoking of marihuana. The anxiety felt as an initial effect with both drugs can be ascribed to changes in proprioceptive perceptions, with consequent damage to the "body image." The addition of visual hallucinations causes an increase in the fright reaction, approximating panic. These hallucinations are zooscopic and reminiscent of delirium tremens. At times the peyote-induced anxiety reactions merge into a psychotic picture.

The cult, or religion, of peyote among the Indians of the Southwest (Piutes, Utes and Navajos) has as its essence the conferring of power by Father Peyote on all its adherents—power to cure illness, bad habits and idleness. In their combat with deep, unconscious anxieties, the Indians, constantly battling a stern and harsh nature, found peyote an instrument for making life tolerable through its conferring on a man power which he would not otherwise possess. The religion also serves the secondary purpose of hiding from public view a sense of inferiority engendered by a clash of cultures. It is through these psychologic mechanisms, as well as by a direct effect on the cerebrum and the thalamus, that the secondary stage of euphoria and contentment is produced in the Indian user of the drug.

CHODOFF.

EVALUATION OF COMPLAINTS AFTER HEAD INJURY. OTTO KANT, J. Nerv. & Ment. Dis. **97**:542 (May) 1943.

Kant points out the difficulty of determining whether post-traumatic complaints are the direct effect of concussion or are due to a superimposed traumatic neurosis. Encephalographic and electroencephalographic studies are of limited help. Although the main complaints, headache, dizziness, irritability and inability to concentrate, are the same whether they are of somatogenic or of psychogenic origin, it is of great importance to differentiate between the two categories, since the former requires indulgence and curtailment of activities, while persons with psychogenic disturbances should be encouraged to discard their complaints and increase their activities.

In the absence of objective signs of damage to the brain, the examining physician must depend on the patient's subjective account of his complaints and their causal relation to the injury. To evaluate the symptoms properly it is important to determine their place in the setting of a given personality. Just how the symptoms express themselves is as important as their nature.

With somatogenic symptoms the personality as a psychologic phenomenon is not involved at all. Such symptoms lack all expressive quality, are little influenced by interference in the psychologic sphere and give the impression that the personality itself is not involved. They appear "foreign" to the personality and give an impression of genuineness, as opposed to psychogenic symptoms, which have expressive value, appear somewhat nongenuine and are characterized by changeability and suggestibility toward psychologic interference.

The patient with a somatogenic disorder tends to belittle his complaints, while the patient with a psychogenic condition exaggerates his suffering. The former is irritable in outbursts, without apparent reference to his emotional situation, while the latter appears gradually to work himself up into a temper tantrum.

Patellar and ankle clonuses may appear with both types—with the organic form clonus is of constant rhythm and amplitude, while with the functional type it is characterized by crescendo and decrescendo and by sudden interruptions. The influence of distraction is of value in differentiation of a Romberg sign of psychogenic and one of somatogenic origin. The former can often be made to disappear by a sudden, harsh command or by having the patient exercise with his arms.

Actual scores in intelligence tests are of no value in the differential problem, but the method by which the patient achieves his score is of importance. Exaggeration and dramatization of a defect are characteristic of the psychogenic type, as is the contrast between the patient's inability to carry out simple intelligence tasks and his excellent orientation and practical judgment in the ward. Genuine fatigability of somatogenic type shows a steady curve of decline of importance, while that of the psychogenic type is sporadic. CHODOFF.

A STUDY OF THE PERSONALITIES OF TWO HUNDRED AND EIGHTY-NINE ABNORMAI DRINKERS. WILLIAM FLEESON and EDWIN F. GILDEA, Quart. J. Stud. on Alcohol **3**:409 (Dec.) 1942.

Fleeson and Gildea point out that there are three groups of abnormal drinkers, with certain differences existing among them. These groups are designated as follows: 1. Primary addicts. These are abnormal drinkers who use alcohol as an aid in adjustment to their environment and are unable to give up its use in spite of insight. It was found that the average age of such drinkers at the time of admission to the hospital was lower than that of the other two groups. The incidence of addicts who were without psychoses on admission was higher than that of the other drinkers. A great predominance of psychopathic personalities was noted among this group. Polyneuropathy was found to be twice as frequent among addicts as among symptomatic drinkers. 2. Symptomatic drinkers. Drinking in this group is evidence of a deep-seated maladjustment, which may break through at any time in the form of a clearly defined clinical entity, such as schizophrenia epilepsy or manic-depressive psychosis. 3. Exogenous drinkers. The drinking of this group is primarly determined by exogenous factors, such patients presenting recognizable signs of chronic overindulgence in alcoholic beverages. Signs of prolonged drinking are deterioration of personality, delirium tremens and the Korsakoff syndrome. Persons with chronic alcoholism drink for various reasons, but by and large because their associates do and they are able to make personality adjustments to their drinking habits even though they show physical signs of overindulgence. They break down with psychoses or near psychoses, lose control of themselves and are sent to the hospital.

LESKO, Bridgeport, Conn.

NEUROPSYCHIATRIC PROGRAM FOR A REPLACEMENT TRAINING CENTER. LELAND E. STILLWELL and JULIUS SCHREIBER, War Med. **3**:20 (Jan.) 1943.

Stillwell and Schreiber present a clearcut and effectively used neuropsychiatric program in a replacement training center. The setup is as follows: 1. A ward is maintained in the station hospital where patients requiring hospitalization for neurologic or psychiatric disorders are studied and cared for until proper disposition is made. 2. A neuropsychiatrist is available for consultation with the other physicians at the hospital. 3. A special training unit is maintained, to which are sent the following types of men: (*a*) mentally normal soldiers who are naturally slow in learning or who manifest poor coordination, (*b*) illiterate soldiers, (*c*) soldiers with language problems, (*d*) soldiers with oligophrenia, (*e*) soldiers with psychoses, (*f*) soldiers with psychopathic personalities, (*g*) neurotic soldiers and (*h*) soldiers with physical disorders.

Any soldier proposed for the special training unit is seen by the psychiatrist together with representatives of the special training unit and of the personnel section in order that his suitability for special training may be determined.

4. A neuropsychiatrist maintains a clinic to which any unit commander may send any of his soldiers whom he considers to be suffering from a personality disorder. From time to time unit commanders are given talks to instruct them in the manifestations of neuropsychiatric disorders.

5. Close cooperation exists between the military police and the neuropsychiatrist in order that chronic guardhouse residents may be studied. Red Cross workers are of valuable assistance in obtaining social data and other pertinent material.

6. The neuropsychiatrist helps to see that morale is maintained. The best means is the provision of a systematic program of education as to the fundamental issues of the war and the arousal in the soldier of a social consciousness, such as he had never known before. Men who are imbued with a zeal which springs from a full knowledge of what they are fighting for are less apt to experience emotional disturbances or other personality disorders as a result of actual warfare.

PEARSON, Philadelphia.

Diseases of the Brain

OPTOCHIASMIC ARACHNOIDITIS. EDWARD R. RYAN, Arch. Ophth. **29**:818 (May) 1943.

Ryan reports 3 cases of chiasmic arachnoiditis, confirmed at operation, in which the symptoms were different.

Of the 3 cases, the first offered a difficult problem in diagnosis. The case was that of 7 year old boy with but one complaint—progressive impairment of vision for two years. The bilateral central scotomas and the atrophy of the optic nerves were accompanied by roentgenographic evidence of destruction of bone in the posterior wall of the right orbital canal, with a normal sella turcica. Operation did not improve the patient's visual acuity.

The second case was that of a 9 year old boy whose only complaint was poor vision in the right eye for three months, with rapid progression of the process during the month before examination. The only signs were papilledema in the right eye, with extensive depression of the visual field in that eye, more advanced in the temporal half, and pronounced depression of the field in the left eye. The diagnosis was confirmed surgically. After operation the fields of vision widened to a notable degree, and vision in the right eye improved from 0.1, prior to operation, to 0.4, after operation; in the left eye vision after operation was slightly less than that present before surgical intervention. Secondary optic nerve atrophy became established after the operation.

In the third case, that of a man aged 34, examination showed normal fundi with bitemporal field defects, more pronounced on the right side. The sella was normal, but the optic foramens were pathologic. The right optic foramen measured 5 by 6 mm., and its margins were decalcified; the left optic foramen measured 4.5 by 4.5 mm., and the margins were clear. After operation and confirmation of the diagnosis, the fields showed an enormous expansion on both sides.

SPAETH, Philadelphia.

MICROPSIA AND TELEOPSIA LIMITED TO THE TEMPORAL FIELDS OF VISION. MORRIS B. BENDER and NATHAN SAVITSKY, Arch. Ophth. **29**:904 (June) 1943.

Bender and Savitsky report a verified case of epidermoid in the chiasmal region, in which the temporal fields of vision presented island-like areas of micropsia and teleopsia and, in addition, a tendency to rotate the plane of the image though the last-mentioned phenomenon was not as sharply limited to the temporal field as were the first two. As a matter of fact, the metamorphopsia was best seen in the apparently normal nasal field.

The case is interesting in that it illustrates specific visual defects in the fields of vision which indicates that the origin of the optic disturbance was peripheral rather than in the occipital cortex.

SPAETH, Philadelphia.

CEREBRAL AIR EMBOLISM. LEO RANGELL, J. Nerv. & Ment. Dis. **96**:542 (Nov.) 1942.

Rangell reviews the literature on the postpartum occurrence of air embolism, especially after the assumption of the knee-chest position during the puerperium. He reports what he believes to be the first case of nonfatal cerebral air embolism following assumption of the knee-chest position. The embolism occurred during the seventh postpartum day in a woman aged 24 and was marked by sudden loss of consciousness, followed by jacksonian convulsions and later by a psychotic state. The patient was hallucinated, felt herself floating and described everything as rotated at exactly 90 degrees. Abnormal neurologic signs were few. The patient made a complete recovery. The symptoms were thought to be the result of cerebral air embolism following the introduction of air into the circulation through the dilated and patent uterine veins.

The author discusses the arterialization of intravenous air and cites several cases from the literature in which, post mortem, air was observed in the left side of the heart and in the cerebral circulation. He concludes that the air in these cases and in his own case must have passed from the venous to the arterial circulation across the barrier of the pulmonary capillaries.

The symptoms of cerebral air embolism vary widely in individual cases and depend on such factors as the location, number and size of the vessels involved, the extent of the collateral circulation and the importance of the centers supplied by these vessels. Symptoms which have been reported include hemiplegia, monoplegia, convulsions, syncope, vertigo, amaurosis, aphasia, alexia and psychosis. The production of symptoms is due primarily to acute cerebral ischemia, sometimes complicated by perivascular hemorrhages. Therapeutic measures, to be successful, must be instituted almost immediately. They should include efforts toward prevention of further ingress of air, administration of cardiac stimulants and direct removal of air from the right side of the heart. Venesection may be useful. The introduction directly into the right side of the heart of 2 cc. of a solution of epinephrine hypochloride (1:10,000 to 1:1,000) has been suggested. As prophylaxis, the knee-chest exercises used during the postpartum period are contraindicated.

CHODOFF.

ACUTE CRANIOCEREBRAL TRAUMA. F. S. GURDJIAN, J. E. WEBSTER and H. ARNKOFF, Surgery **13**:333, 1943.

The authors report the results of observations at autopsy in 151 cases of death following cranial trauma. The series represents a consecutive, unselected series from the Wayne County morgue, Detroit. Gross evidence of cerebral damage was present in every case, though it was minimal in several instances. In 61 of 133 cases the patient was dead on admission to the hospital, and in 36 instances death occurred within twenty-four hours. The authors confirm the observation that mortality from head injury rises as age increases.

Contusion of the brain was more frequent on the orbital surface of the frontal lobe and over the frontal and temporal poles. There were 191 areas of contusion in 72 of the cases reported. Petechial hemorrhages were noted on gross examination in 54 cases. There were 22 instances of acute subdural hematoma, 11 cases of epidural hemorrhage and 1 case of chronic subdural hematoma, representing a total of 21.5 per cent of the entire group of 151 cases studied. These 34 lesions were of sufficient size to be regarded as operable. The authors conclude that hemorrhage producing a cerebral mass lesion is frequent after trauma. Hemorrhages of nonsurgical magnitude (under 30 Gm.) were observed in the subdural space in 12 additional cases and in the epidural space in 4 more cases. They were observed in the frontoparietotemporal region in 30 of 34 cases of subdural hemorrhage and in 8 of 11 cases of epidural bleeding. In all the cases of surgical subdural hematoma the lesion was unilateral. Fracture of the skull was present and on the same side as the lesion in all cases of epidural hemorrhage; it was commonly absent with subdural hematoma. In 8 cases it was found that the subdural hematoma was on the

side opposite the line of fracture. In 39 cases there was no fracture of the skull. In 19 of these 39 cases death occurred in the absence of any injury except the cranial trauma. The authors conclude therefore that "the presence or absence of a fractured skull as a criterion of the severity of cerebral injury would seem to be a loose standard." Concomitant injuries were often masked by unconsciousness. They were held responsible for death in 7 of 94 cases of fracture of the skull and in 9 of the 39 cases in which no fracture was present.

The following clinicopathologic correlations were of interest: Of 10 cases in which a state of consciousness suggested a progressive lesion, a subdural or an epidural hemorrhage was the cause of death in 4; in 4 others a diffuse injury to the brain was present, and in 2 cases fatty cerebral embolism was the cause of death. In the great majority of cases with profound injury to the head no remarkable change in blood pressure and pulse was apparent throughout the period of hospitalization. In 13 the temperature was 105 to 109 F. at the time of death. Respirations were above 40 per minute in 21 cases. The most prominent and puzzling feature of the "neurogenic" pattern of death was tachypnea, with or without pulmonary edema.

SHENKIN, Philadelphia.

Treatment, Neurosurgery

FOLLOW-UP STUDIES OF A SERIES OF PATIENTS TREATED BY ELECTRICALLY INDUCED CONVULSIONS AND BY METRAZOL CONVULSIONS. B. L. PACELLA and S. E. BARRERA, Am. J. Psychiat. **99**:513 (Jan.) 1943.

Pacella and Barrera studied 144 patients treated with electrically induced convulsions and 126 patients treated with metrazol. The therapeutic effects in the two groups were essentially the same, especially in patients with psychoses. The statistics are slightly in favor of electric shock. In view of this and the less undesirable effects with electrical shock, the authors believe that those of metrazol shock should be discontinued in favor of the employment of electric shock. They conclude that convulsive therapy is of great value for the affective psychoses, as compared with the results for schizophrenia. The best results were obtained in patients with depression, feelings of guilt, self depreciation and suicidal tendencies.

FORSTER, Philadelphia.

CONVULSIVE SHOCK THERAPY IN ELDERLY PATIENTS. VERNON L. EVANS, Am. J. Psychiat. **99**:531 (Jan.) 1943.

Evans investigated the results and the risks entailed in convulsive shock therapy in a group of 50 patients over 50 years of age. Of this group, 21 recovered and 19 showed improvement. The results were considered comparable to those obtained in treatment of similar psychoses in younger patients. No patient was refused convulsive treatment because of physical risks alone. Two patients suffered fractures of the humerus, which healed uneventfully. One patient had pneumonia in the course of treatment and died, but this was considered incidental, and not the result of treatment. Evans concludes that the risk of administration of shock therapy to elderly patients is well worth taking.

FORSTER, Philadelphia.

THE ELECTROFIT IN THE TREATMENT OF MENTAL DISEASE. DAVID J. IMPASTATO and RENATO ALMANSI, J. Nerv. & Ment. Dis. **95**:395 (Oct.) 1942.

Impastato and Almansi describe the essential features of the apparatus used in the production of the electric fit. They advocate the use of a constant time interval of one-tenth second and an increase of the voltage rather than of the time when a stronger stimulus is necessary. The authors believe that this minimizes the danger of cardiac accidents. The method may be used for patients with manic-depressive psychosis, schizophrenia, involutional psychosis and severe psychoneuroses, and possibly certain organic psychoses. Patients should be free from severe constitutional disease and may be up to 60 years of age. Treatments should be given with the patient in hyperextention, in which position the danger of fracture of the spine is almost nil. At the beginning of therapy the authors attempt to establish the individual convulsive threshold. They then increase the voltage sufficiently to produce a grand mal seizure. Two treatments a week are given until recovery, which is followed by one or two more treatments. The responses which may be obtained are classified as follows: (1) the conscious reaction, in which the patient does not lose consciousness; (2) a blank, characterized by fleeting unconsciousness and sudden flexor spasm; (3) petit mal, with a longer period of unconsciousness, more violent spasm and retrograde amnesia, and (4) grand mal, characterized by initial flexor spasm, a period of apnea, a tonic and a clonic phase, a second period of apnea and postconvulsive phenomena. For patients who thrash about after the attack 3½ grains (0.227 Gm.) of sodium amytal may be given intravenously. Electroencephalographic changes associated with the electric fit are identical with those associated with metrazol seizures except that the abnormal activity following the electric convulsion lasts a shorter time. The authors enumerate a number of advantages of the electric fit over the metrazol convulsion, one of the most important being the complete amnesia for the treatment, so that patients do not object to continuing treatment. Of 50 patients who completed treatment, 80 per cent in the manic-depressive group and 50 per cent in the schizophrenic group recovered or showed improvement. Fewer complications were seen with the electric shock method than with the metrazol method. Those noted were dislocations of the jaw, fracture of the fifth dorsal vertebra and, in 1 patient, severe pains in the muscles of the arm. Transient loss of memory, depersonalization and confusion may be expected during periods of treatment and are not of bad prognostic import.

CHODOFF.

OBSERVATIONS ON THE KENNY TREATMENT OF POLIOMYELITIS. F. H. KRUSEN, Proc. Staff Meet., Mayo Clin. **17**:449 (Aug. 12) 1942.

The Kenny concept of poliomyelitis is apparently in no conflict with the accepted proof of damage to the anterior horn cells and flaccid paralysis. It asserts, however, that early in the disease the major symptoms are not so much flaccid paralysis as "muscular spasm," "incoordination" and "mental alienation."

Krusen found that muscular spasm occurs during the early stages of poliomyelitis, that it may be widespread and that it is something more than the result of meningeal irritation, as was previously thought. The principal sites of such spasms are the hamstring muscles; the muscles of the back and neck; the gastrocnemius, pectoral, quadriceps and biceps muscles, and the muscles of respiration. The Minneapolis investigators of the Kenny concept define muscular spasm as a group of symptoms, including fibrillary twitchings (fasciculation), hyperirritability of the muscle to stretching and a more or less tonic state of contraction of the muscle fibers, which frequently cannot be overcome even by great force.

Incoordination is defined as "(1) that due to the spreading of motor impulses intended for a certain muscle to other muscles or groups of muscles due to

such conditions as pain on attempted motion of the involved muscle or inability of that muscle to perform its proper function; (2) that occurring within the involved muscle itself, so that ineffective contraction is produced instead of a coordinated rhythmic contraction producing maximum motion at the insertion of the muscle."

Mental alienation is defined as "inability to produce a voluntary, purposeful movement in a muscle in spite of the fact that the nerve paths to that muscle are intact. This is a physiologic block which must be distinguished from the organic interruption resulting from the destruction of anterior horn cells by the disease." The Minneapolis workers suggest that the most frequent mechanisms for the production of mental alienation may be stated as follows: 1. A muscle is pulled beyond its normal resting length by its opponent, which is in spasm. 2. A muscle may become "alienated" when pain is produced in its involved opponent by the attempt of such unaffected muscle to contract. 3. The spasm, or its subsequent results, in an affected muscle may be so severe that the braking action, or check, on the normal, opposing muscle may discourage the latter enough to produce its "alienation." 4. The disease may produce changes in the nervous system which do not actually destroy the cells or fibers but cause loss of conduction power and interfere with normal neuromuscular action. Thus, in the case of foot drop, the gastrocnemius muscle is the one affected and is to be regarded as in spasm, the dorsiflexors of the foot suffering from "mental alienation."

Krusen asserts that "the tremendous enthusiasm for the Kenny procedure seems to a large degree warranted, although it appears evident that some of the claims concerning it are too enthusiastic." The claim that no deformities follow the procedure seems untrue, since deformities appear to develop in some cases. Krusen agrees that contractures, malalinements and spinal curvatures do not follow the treatment.

ALPERS, Philadelphia.

Muscular System

DIAGNOSTIC TESTS FOR MYASTHENIA GRAVIS WITH PROSTIGMINE AND QUININE. L. M. EATON, Proc. Staff Meet., Mayo Clin. **18**:230 (July 14) 1943.

Eaton discusses the use of prostigmine and quinine in the diagnosis of myasthenia gravis, the only disease known to be relieved by the first drug and made worse by the second. Prostigmine is always given first, in doses varying with the prominence of objective signs of weakness. Emphasis is laid on the use of quinine as an adjunct to the prostigmine when response to the latter is not conclusive. The dose of quinine sulfate has not been generally established, but before myasthenia is ruled out at the Mayo Clinic 10 grains (0.65 Gm.) is given three times a day at two or three hour intervals.

Three case histories are cited, in 2 of which responses to prostigmine were doubtful but were made much weaker by administration of quinine sulfate the same day. In the third case the strength was increased by both drugs. In the last case there was no objective weakness to begin with; so the change was judged merely on the subjective report.

The test may be applied in any case of objective weakness, whether generalized or localized to one or a few muscles, regardless of the age or sex of the patient. When there is no objective evidence of myasthenia particular care must be taken, especially if prostigmine is given alone to a hysterical patient. Such a patient may be helped as much by a placebo or, as shown by the third case, by the use of quinine after prostigmine.

MCCARTER, Philadelphia.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President*

Regular Meeting, May 20, 1943

Homonymous Hemianopsia: Report of Two Unusual Cases. DR. JOSEPH A. LUHAN.

CASE 1.—F. C., a naturalized Mexican aged 30, became acutely ill, when he collapsed on the street. Shortly after his admission to the Cook County Hospital, on Jan. 2, 1942, he presented mental torpor, nystagmus, a Babinski sign bilaterally, right homonymous hemianopsia with macular sparing, fleeting astereognosis on the right side and blurring of the right optic disk. About a month after the onset of illness spastic paraparesis inferior, with a sensory level at the seventh thoracic dermatome, developed within a few days. This later receded, until in another month he became ambulatory, and soon thereafter the hemianopsia disappeared. Five months after onset of his illness no gross hemianopsia was apparent in confrontation perimetric tests, although peripheral visual acuity was diminished in the right fields. Except for spastic weakness in the right leg, there were no residual neurologic signs. The course of this man's illness was that of a demyelinating disorder allied to multiple sclerosis (so-called acute disseminated encephalomyelitis), if not actual disseminated sclerosis. Homonymous hemianopsia ordinarily connotes a neoplastic or vascular origin. This case is reported because of the rarity of production of such defects of the visual fields through the agency of inflammatory or demyelinating processes.

CASE 2.—M. D., a man aged 30, whose maternal grandmother and mother had each suffered from ophthalmic migraine, had himself experienced many attacks of typical and severe ophthalmic migraine since the age of 16. On July 5, 1942 he had a sudden onset of numbness of the left side of the jaw and the left arm, left hemiparesis, pronounced blurring of vision and crude hallucinations of light and pain in the right temple. The paralysis and numbness wore off in half an hour, when vision returned except for blurring in the left homonymous fields. On July 11 a second, identical attack was followed by even greater residual loss of vision in the left fields. No further attacks, or any which might be construed as migrainous, have occurred since. On April 4, 1943 the left visual fields showed large bilateral scotomas reaching to the midline but partly sparing the macular area. Careful examination, including such laboratory aids as spinal puncture and roentgenographic studies, disclosed nothing abnormal except for this hemianopsic defect of the visual fields. The case evidently is one of a cerebral vascular accident complicating ophthalmic migraine, and it raises the question whether there may have occurred an encephalomalacic sequel to prolonged vasospasm during the course of a severe migrainous seizure.

News and Comment

APPOINTMENT OF DR. S. EUGENE BARRERA

The Albany Medical College and the Albany Hospital announce the appointment as of Jan. 1, 1944 of Dr. S. Eugene Barrera as professor of neurology and psychiatry and neurologist and psychiatrist-in-chief. The professorship of neurology and psychiatry carries with it the directorship of the department of neurology and psychiatry and of Mosher Memorial, which is the psychiatric unit within the department. Dr. Barrera was formerly principal research psychiatrist of the New York State Psychiatric Institute and Hospital, and also assistant professor of psychiatry of Columbia University College of Physicians and Surgeons. In the new appointment, he succeeds Dr. D. Ewen Cameron, who becomes professor of psychiatry at McGill University, Montreal, Canada. Dr. Barrera has been the author and co-author of numerous papers on neurologic and psychiatric subjects.

NATIONAL COMMITTEE FOR MENTAL HYGIENE

The National Committee for Mental Hygiene announces the establishment of a fund for research in psychosomatic medicine. The purpose will be to stimulate and subsidize research in the psychosomatic aspects of the diseases chiefly responsible for disability and death. The fund will be directed by Dr. Edward Weiss. Projects will be considered by the following committee: Dr. Charles M. Aldrich, Dr. Franz Alexander, Dr. Stanley Cobb, Lieutenant Colonel William C. Menninger and Dr. John Romano. The fund will be administered under the direction of Dr. George S. Stevenson, National Committee for Mental Hygiene.

Communications should be addressed to Dr. Edward Weiss, *269* South Nineteenth Street, Philadelphia 3.

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

The following candidates, who previously passed the examination for membership in the American Board of Neurological Surgery, have now met the Board's requirement of two years' practice in neurologic surgery and have received their certificates, as of March 26, 1944:

Dr. James G. Arnold Jr., Baltimore; Dr. Samuel Lowis, Boston; Lieut. William Nosik (MC) U.S.N.R.; Lieut. Axel Olson (MC) U.S.N.R.; Capt. James L. Thomson, Medical Corps, Army of the United States, and Dr. C. Robert Watson, Brooklyn.

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

The American Board of Neurological Surgery will hold an examination on June 5, 1944 at the Illinois Neuropsychiatric Institute, 912 South Wood Street, Chicago.

CORRECTION

In the article by Dr. Robert Wartenberg entitled "Studies in Reflexes: History, Physiology, Synthesis and Nomenclature: Study I," in the February issue (ARCH. NEUROL. & PSYCHIAT. **51**:113, 1944), the following corrections should be made:

On page 115, second column, in the seventh line from the top, the word "reflex" should be "reflexive."

On page 132, first column, in the third line in the first paragraph under the center head "Finger-Thumb Reflex (Mayer)," "metacarpophalangeal reflex" should be changed to "basal joint reflex."

On page 133, fifth line from the top of the second column, "diagnosis of an early lesion" should be changed to "early diagnosis of a lesion."

Book Reviews

Medicine and the War. Edited by William H. Taliaferro, M.D. Price, $2. Pp. 193. Chicago: University of Chicago Press, 1944.

This series of ten lectures on "Medicine and the War," given by members of the faculty of the University of Chicago, were intended for student groups and are discussions of a series of medical problems highlighted by the war. The science and art of medicine play a most important role in modern warfare.

The first lecture by Dr. Arno B. Luckhardt is a historical review of the role of medicine in war. This is followed by a consideration of food as a basic fuel for both soldier and civilian in wartime. Another lecture reviews the recent advances in chemotherapy, especially the sulfonamide compounds, antimalarial agents, penicillin and thyrothricin. Dr. William H. Taliaferro's survey of the problem of malaria is excellent and indicates that malaria is the most important infectious disease in the present war. Dr. Clay G. Huff reviews the problems related to changes in modern transportation and how airplane travel can afford unwanted aid in the dissemination of diseases and disease-carrying insects. Dr. Alexander Brunschwig considers the problem of shock and blood substitutes. Aviation medicine is a new field of medicine, with its own physiologic and psychologic problems. The problems of anoxia, speed and acceleration and pilot fatigue and black-out make fascinating reading for the physician. Other lectures deal with the neurologic and psychologic effects of cerebral injuries, psychiatry and the war and chemical warfare.

These lectures stress the need for scientific research in development of better methods for saving life in war and emphasize the numerous ramifications of medicine in war. It is highly recommended as an important and timely contribution.